VOLUME 59 • MAY 1958 • NUMBER 5

OPHTHALMOLOGY

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A Suturing Spatula
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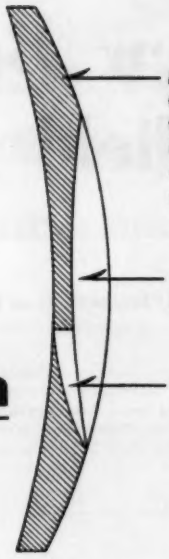
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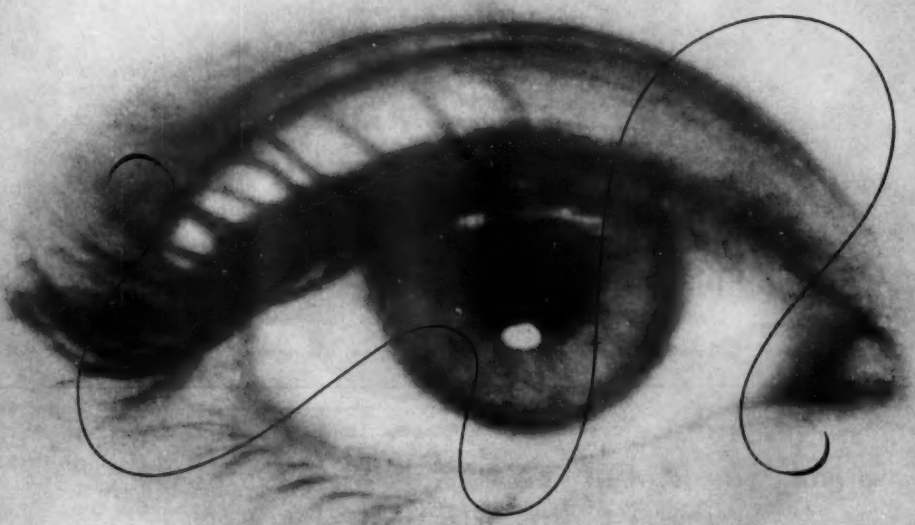

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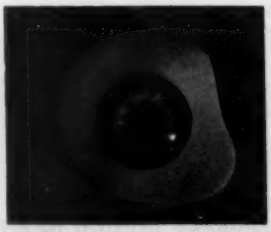

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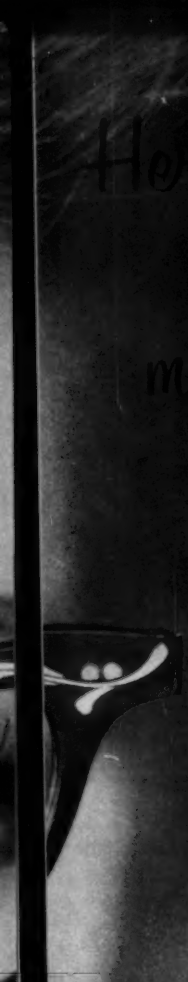

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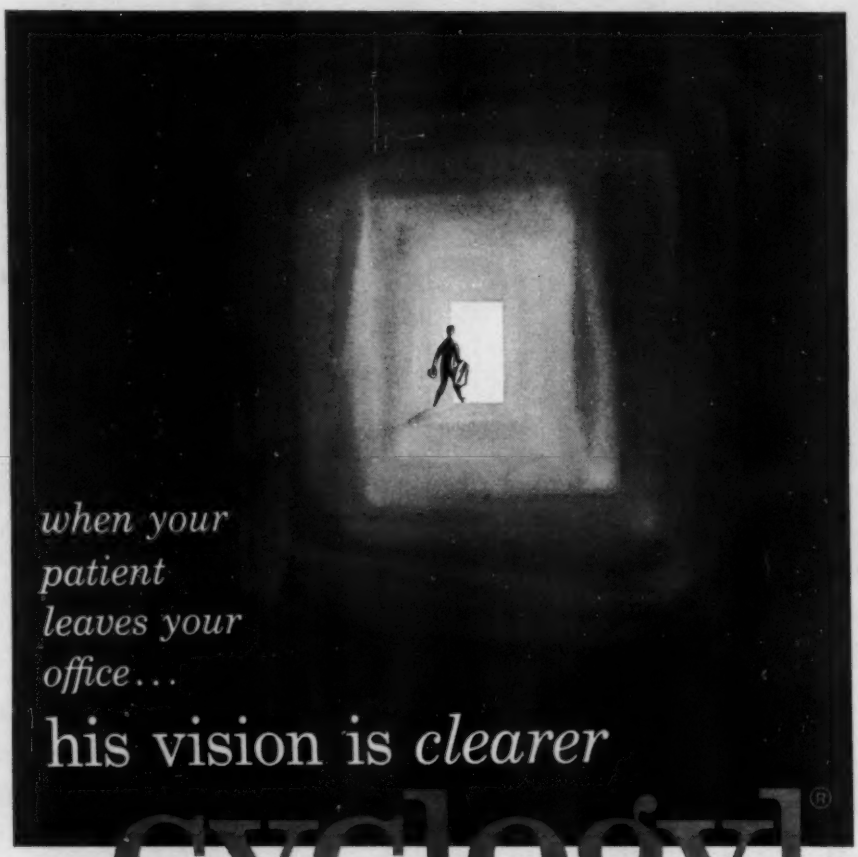

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On the Correction of Unilateral Aphakia with Contact Lenses

KENNETH N. OGLE, Ph.D., Rochester, Minn.; HERMANN M. BURIAN, M.D., Iowa City, and ROBERT E. BANNON, B.S., Southbridge, Mass.

Introduction

During the past two decades, but especially during the last 10 years, there has appeared in the literature an increasing number of articles and discussions dealing with the clinical results of the correction of unilateral aphakia with contact lenses.

Certain findings of clinical interest emerge from the study of these reports. One impression is that aphakic eyes would seem to tolerate contact lenses better than eyes not operated on.[1,9,11,20,21] Goar attributes this to a reduction in corneal sensitivity of the operated-on eyes. On the other hand, Constantine and McLean do not think that there is such a reduction in the corneal sensitivity of the eyes of their patients. If, instead, the better tolerance could be attributed to the fact that these patients received sufficient benefit from the wearing of contact lenses to increase their willingness to wear them, this might be considered a strong argument in favor of the clinical value of such lenses.

The second impression is that more and more favorable reports are appearing, stressing the reestablishment of comfortable single binocular vision in patients with unilateral aphakia corrected by means of contact lenses. However, there is no unanimity in this respect, since the conclusions drawn about the value of such corrections differ widely. Cowan insisted on theoretical grounds that comfortable, normal binocular vision could not be obtained with this procedure. Mann found that only 2 (actually, only 1 without question) of 10 patients had gained binocular vision. Cross noted that a larger proportion of patients with unilateral aphakia had given up the wearing of contact lenses than had the patients in his series who had been given contact lenses for other reasons. On the other hand, Schlosshardt, Blum, Constantine and McLean, Rougier, Goar, Györffy, Ridley, and others have found that a large percentage of their patients achieved a remarkably high degree of binocular cooperation.

For a number of reasons it is difficult to assess the value of these more optimistic reports. The criterion of success or failure is usually based on the subjective responses of the patients during relatively short periods of observation. No satisfactory follow-up studies have as yet been made. Most important, truly appropriate tests for functional binocular vision, as would be required in the situation, have not been employed. It will be shown later that the Worth

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four-dot test, the Hering falling-bead test, simple tests for stereopsis, and even tests with the synoptophore are not adequate to give a full description of the binocular status of these patients. Against this it must, however, be pointed out that a number of authors have observed a very significant reduction in manifest or latent deviations, both horizontal and vertical, following the wearing of contact lenses in cases of unilateral aphakia.[9,18,26] Foley has found in the orthoptic examination of such patients that an excyclophoria was present in 43% at the initial examination, whereas the percentage dropped to 18 in follow-up examinations. Such recoveries of the alignment of the eyes offer cogent, though indirect, evidence for the presence of binocular cooperation.

Almost none of the papers reviewed discuss the optical and physiologic aspects of the correction of unilateral aphakia, and none of them deal adequately with these aspects, although the various problems involved in the restoration of single binocular vision to these patients are pointed out in most of the papers.

These problems and difficulties are four in number. One consists in the greater or lesser degree of suppression, or, conversely, readiness to regain binocular vision, exhibited by these patients. The tendency toward abnormal suppression is in general the greater, the longer one eye has been excluded from the binocular act of vision. The age of the patient at which the cataract occurred may also be of significance, but there are in addition unexplained individual differences.[26,33] Lyle and Ridley have emphasized the need of a study of the suppression pattern in these patients, and Lyle has set a favorable result of an orthoptic evaluation as the criterion for recommending or rejecting the use of contact lenses in unilateral aphakia. The figures supplied by Foley are interesting in this respect. She found among 90 patients examined orthoptically that 50 presented abnormal suppression. Of these patients, 22 were rejected and 28 were given contact lenses. Of the 19 of those in whom the work was completed, 10 demonstrated binocular vision on reexamination while 9 did not. Thirty-nine patients were diagnosed as "non-suppressors." All these were given contact lenses. Of the 32 who had been reexamined at the time of the report, 28 had binocular vision and only 4 did not.

The second difficulty arises in unilateral aphakia because of the fact that the phakic eye is capable of exerting normal accommodation whereas the aphakic eye is not. This point has been stressed by Cowan and by Cross, who feel strongly that this is a major obstacle to the patients' comfort, while Hirtenstein does not consider it to be significant. According to the latter author, unilateral cycloplegia has no effect on the fusional amplitudes. It would indeed appear that the absence of effective accommodation in the aphakic eye has no deleterious effect either on the subjective response or on the binocular cooperation in these patients. The proper handling of this situation from an optical standpoint will be mentioned later in this paper.

The third difficulty consists in the differential prismatic effect which is produced when a unilateral aphakia, or any other extreme anisometropia, is corrected by spectacle lenses. Contact lens correction effectively eliminates this difficulty, a fact which will not be considered further in this paper.

The fourth, and principal, problem in the correction of unilateral aphakia which must be solved before the reestablishment of physiologic binocular vision can become possible is the necessity of making the magnification of the retinal images in the two eyes as nearly equal as possible. The existence of this problem has been recognized in the past, and the introduction of contact lenses has allowed one to come to grips with it much more effectively than has heretofore been possible. However, it is not correct to state, as does Ridley, that contact lenses restore iseikonic conditions even in gross anisometropia. It will be

shown by theoretical considerations that a large amount of residual aniseikonia will have to be expected in almost all the cases. This amount can be measured, but estimates based on simple comparative size judgments on the part of the patients, as reported by Girardet and by Rougier, have no valid basis. The only actual measurements reported thus far in the literature were made by Dufour, who measured a residual aniseikonia of 7% in one patient, and by Linksz, as reported by Constantine and McLean, who found in seven patients a residual aniseikonia of 4%, 6%, 7%, 8%, 8.5%, 9%, and 10%, respectively.

We became interested in the theoretical and clinical aspects of the problem of the correction of unilateral aphakia in 1938, when we were collaborating in the former Dartmouth Eye Institute. We did not publish our work done then and in the following years because we had hoped to include a greater number of patients in such a report. Further developments beyond our control made this impossible, but the material then collected is still pertinent to the problem. Because of the great practical significance of unilateral aphakia and of the lack of theoretical studies in the literature, we are presenting this paper, the purpose of which is to review the essential aspects of the problem concerned with the relative magnification of the images in the two eyes; to review the physiologic problems involved and to answer the question of how patients who, according to the reports in the literature, have regained comfortable binocular vision cope with the large amount of residual aniseikonia after correction of unilateral aphakia with contact lenses, and, lastly, to point out what studies are indicated for the further clarification of the problem.

Optical Theory of the Magnification Problem

The basic theory of how the retinal image will be magnified when the refractive error in aphakia is corrected by lenses is a simple one.[30] Reduced to the essentials, it may be presented as follows: Suppose we have a normal emmetropic eye in which, for some reason, it is necessary to remove the crystalline lens surgically. Now, from a purely optical point of view, the removal of this crystalline lens renders the eye hyperopic, just as would the insertion of a thin lens of minus power at the optical center of the crystalline lens in the normal eye. The power of this minus lens would be of such order as to neutralize completely the refractive power of the crystalline lens. The farsightedness caused by this minus lens (as in aphakia) is then usually corrected by a spectacle lens in front of the eye at a certain distance h from what was the effective optical center of the crystalline lens before operation. Now, the power of this correcting spectacle lens (which we shall for the moment consider also a "thin" lens) must be such as to completely offset the power of the hypothetical minus lens placed in the eye. The correcting (plus) spectacle lens and the hypothetical (minus) lens constitute a simple Galilean telescope, an afocal system. Such an optical device magnifies the image seen through it. If the vertex power of the correcting lens is V_e diopters (D.), one can write down the formula for this magnification as $P=1\div(1-V_eh)$. For example, a lens of 11 D. power is placed 14 mm. from the cornea to correct the formerly emmetropic and now aphakic eye. The distance of effective optical center of the crystalline lens from the cornea is about 5.7 mm.; thus, h is about 19.7 mm., or 0.0197 meter. The magnification of the retinal image as compared to that before the operation would be $P=1\div[1-(11)(0.0197)]=1\div(1-0.217)=1\div0.783=1.28$, or an increase in magnification of the retinal images of 28%. This magnification, P, is due solely to the power of the correcting spectacle lens, V_e, and its distance, h, from the "seat" of the aphakia, and, accordingly, has been designated the "power factor" in the total magnification of the retinal image.

Now, the nearer the correcting lens is to the cornea (the smaller h becomes), the less

the magnification will be. The limiting situation will obtain when this correcting lens is in contact with the cornea, and the limiting distance from the "seat" of the aphakia will be about 5.7 mm. We must, of course, increase the power of the correcting lens as it is brought closer to the eye, to keep the eye fully corrected. If the correcting spectacle "thin" lens has a power of 11 D. and is at 14 mm. from the cornea, then the power of a lens in contact with the cornea would have to be $V=V_o \div (1-V_o h)=11 \div [1-(11)(0.014)]=11 \div (1-0.154)=11 \div 0.846=+13.0$ D. The magnification of the retinal image when the "thin" correcting lens is in contact with the cornea, due to the power alone, would then be $P_c=1 \div [1-(13)(0.0057)]=1 \div (1-0.074)=1 \div 0.926=1.08$, or a magnification of the image of 8%. This would be the least magnification to be expected from the correction by a "thin" contact lens of an aphakic eye which had been emmetropic prior to operation. Thus, by correcting the aphakia with a "thin" contact lens instead of with a "thin" ophthalmic spectacle lens, the magnification of the retinal image has been reduced from 28% to 8%, a result already pointed out by Hartinger, Emsley, Haas, Bürki, and others.

But since the corrective lens is not infinitely thin, an additional magnification due solely to its thickness and to the curvatures of its front and back surfaces (the shape magnification factor) also contributes and adds to the total magnification of the retinal image. Boeder has fully discussed the contribution of the dimensions of the Dallos form of contact lens with "fluid lens" to the total magnification of the image. With this form of contact lens, he found that the magnification would be increased above that due to the power of the correction lens alone, by an amount between 2.7% and 5.1%. We may consider, for the purpose of our discussion, that the contact lens consists of an afocal lens system, to the posterior surface of which is added an infinitely thin lens having the necessary power to correct the aphakia in contact with the cornea. The per cent magnification of the retinal image of the aphakic eye, which before operation was emmetropic, is approximately the sum of the per cent magnifications of two factors, the first of which, the shape factor, depends only on the dimensions of the correcting lens (as an afocal system) and the second of which, the power factor, depends only on the vertex power of the system and its distance from the seat of the aphakia. This latter factor is the P part of the magnification as defined above.

If we were to use the more recent "minimal clearance" or "fluidless" type of contact lens, the shape factor of the total magnification of the contact lens would still be about 3% to 5%, depending on surface curvature and thickness. Thus, the total magnification of the retinal image, when the hyperopia of an aphakic eye which had been emmetropic before operation was corrected by a contact lens, would be about 11% to 13% (as Boeder has already shown).

Whether the contact lens used to correct the unilateral aphakia will at the same time reduce or eliminate the aniseikonia arising from that correction and from the correction of the refractive error of the unoperated-on eye will depend on the following factors.

(1) The refractive error of the cataractous eye prior to the operation and before the onset of any indicial myopia due to nuclear sclerosis and, particularly, also on whether that error was axial or refractive in origin.[30]

(2) The refractive error of the fellow (phakic) eye and, in addition, whether that error is of axial or refractive origin and whether it is corrected by a spectacle lens or by a contact lens.

(3) The possible modification of the refractive power of the cornea following the surgical procedure.[16]

(4) The particular dimensions chosen for the curves and thicknesses of the contact lenses. Within certain narrow limits, fixed by the radius of curvature of the cornea, the

refractive error to be corrected, and the type of contact lens chosen, it is possible to vary the curvatures and thicknesses of the lens to vary the shape-factor part of the total magnification.

The role played by the refractive error of the eye prior to the operation in relation to the resultant magnification of the retinal image when the hyperopia due to the aphakia is corrected with a contact lens is an important one. Hartinger and Rugg-Gunn have already called attention to the fact that for a previously axially myopic eye, when the aphakia was corrected by a contact lens, the resultant magnification of the retinal image would be much greater than if the eye had been emmetropic. We cannot know, of course, in any given patient whether the initial ametropia is axial or refractive in origin or how much the operation may have altered the initial ametropia. Any change due to the latter would be a refractive change. Nevertheless, it is instructive to determine what the magnifications, or the relative magnifications between the images of the two eyes, might be on the assumption that the basic ametropias were solely axial or solely refractive in origin.

Axial Ametropia.—As a general rule, when an ametropia is due solely to an error in axial length of the eye and this error is corrected by an ophthalmic lens placed at the anterior focal point of the eye, the resultant magnification of the retinal image is the same as though the eye were emmetropic.[30] When a contact lens is used to correct the error in the same eye, we have effectively moved the correcting lens from some point near the anterior focal point back to the cornea of the aphakic eye, a change in distance of approximately 15 mm. In the axially myopic eye this means an increase in magnification of the order of 1.5% per diopter of the axial ametropia. Conversely, the magnification of the retinal image of an axially hyperopic eye will be relatively decreased with the contact lens correction.

The same principle is at work when contact lenses are used to correct the refractive error of an aphakic eye that had been axially myopic (or hyperopic) before operation. In the Table are given the per cent magnifications of the retinal image that might be expected when the refractive error of the aphakic eye with various axial ametropias before operation is corrected by a "thin" contact lens. These per cent magnifications, which were calculated from a schematic eye, pertain only to the power-factor portion of the total magnification. To these should be added the per cent magnification of about 3% to 5% introduced by the physical dimensions of the contact lens itself. It is clear, therefore, that only when the aphakic eye was hyperopic above 4 D. prior to operation would the resultant change in magnification of the retinal image be small.

Per Cent Magnification (Due to Power Factor Only) of Retinal Image (Relative to That of the Retinal Image in the Emmetropic Eye) for Eyes of Various Axial Ametropias After Cataract Operation and After the Total Refractive Error Has Been Corrected by Contact Lenses

Refractive Error of Eye Prior to Operation, Spectacle Plane, D.	Magnification, %
+6	− 2.5
+5	− 1
+4	+ 1
+3	+ 3
+2	+ 4.5
+1	+ 6
0	+ 8
−1	+10
−2	+11.5
−3	+13
−4	+15
−5	+17
−6	+18

If the refractive error of the unoperated-on, or phakic, eye is also axial in origin, and if this error is corrected with a spectacle lens placed near the anterior focal point of the eye, then the per cent magnifications shown in the Table plus the 3% to 5% will also be approximately the aniseikonia between the images of the two eyes.

If the axial ametropia of the unoperated-on eye is also corrected by a contact lens, then the magnification of the images of the two eyes due to the physical dimensions of the contact lenses alone will be about the same in the two eyes, and so the resultant

aniseikonia will depend only on the power factors of the magnifications and will be greater or smaller than those values given in the Table, depending on the relative powers of the refractive errors of the two eyes. Favorable conditions for equalizing the magnifications are present when the axial refractive errors of the aphakic eye and of the unoperated-on eye are hyperopic above 5 D., both eyes being corrected with contact lenses.

Refractive Ametropia.—The problem of predicting the magnification of the retinal image of a corrected aphakic eye which prior to operation had also a refractive type of ametropia is a little more difficult, because that magnification will depend on where the "seat" of the initial refractive ametropia lay: at the cornea, at the crystalline lens owing to curvature or index changes, or in combinations of these. Unlike the case of axial ametropia, when the refractive ametropia is corrected by a spectacle lens placed near the anterior focal point, there will be a change in the magnification or size of the retinal image compared with that of the emmetropic eye. The retinal image size is increased with plus corrections and decreased with minus corrections. The change, in per cent, is approximately equal to the power of the lens in diopters multiplied by the distance in centimeters of the lens from the "seat" of the refractive ametropia. If the refractive ametropia is due to an error in corneal curvature, then the correction with a contact lens will introduce little or no magnification from the power factor (because $h=0$), but of course there will be the magnification due to the dimensions of the contact lens (shape factor). If the seat of the refractive ametropia was due to curvature or indicial errors of the crystalline lens, then the magnification compared with that of the em-

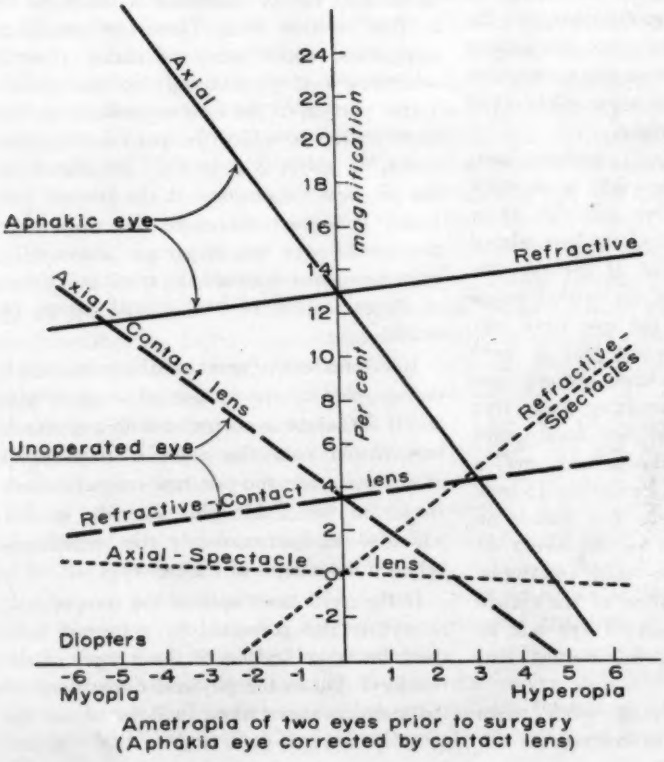

Fig. 1.—Approximate magnifications of the retinal image that might be expected with the correction of axial and refractive ametropia, with contact lens for the aphakic eye and spectacles or contact lens for the unoperated-on eye.

metropic eye will again be greater by about 0.5% for each diopter of refractive error.

We may summarize these rule-of-thumb determinations in the graph shown in Figure 1. The refractive ametropia is taken as being one-half corneal and one-half lenticular. Of necessity, this summary has been much oversimplified. On the abscissa is the ametropia of both the aphakic eye prior to operation (and before the beginning of sclerosis of the lens) and of the unoperated-on eye. The ordinate denotes the per cent magnification of the retinal image to be expected when the ametropia is corrected—the solid lines pertaining to the aphakic eye corrected by a contact lens. The interrupted lines pertain to the correction of the unoperated-on eye (*a*) with spectacle lens and (*b*) with contact lens. The important thing to note is the marked difference in these magnifications depending on the origin of the ametropia and the method of correction. In order that there be no or little aniseikonia following the corrections, the magnification change introduced should be the same for the two eyes.

One notes particularly the following:

1. If the ametropias were about equal for the two eyes and were axial in origin, one would expect an aniseikonia (*a*) varying from 15% in high myopia to about 2% for high hyperopia, if the ametropias of both eyes are corrected by contact lenses, and (*b*) of about 26% for high axial myopia (−5 D.), decreasing to zero for an axial hyperopia of +5 D., when the ametropia of the unoperated-on eye is corrected by spectacle lenses. Thus, high axial hyperopia of both eyes provides the better possibility of eliminating the aniseikonia in the correction of unilateral aphakia with contact lenses in both eyes.

2. If the ametropias were of the same order for the two eyes and were refractive in origin, one would expect an aniseikonia (*a*) of about 10% if the refractive errors of both eyes, regardless of amount, are corrected by contact lenses and (*b*) of about 34% for high refractive myopia (−6 D.), decreasing to about 5% for high refractive hyperopia (+6 D.), when the ametropia of the unoperated-on, or phakic, eye is corrected by spectacle lenses.

3. If the two eyes were emmetropic, one would expect an aniseikonia (*a*) of about 13% if the aphakic eye is corrected by a contact lens and if no "lens" is placed before the unoperated-on eye and (*b*) of about 10% if the aphakic eye is corrected by a contact lens and if a zero-power contact lens is used before the unoperated-on eye.

4. If the ametropias were of the same order for the two eyes and were one-half axial and one-half refractive in origin and if both were corrected with contact lenses, one would expect an aniseikonia of about 9% for 5 D. of myopia or 7% for 6 D. of hyperopia. If the refractive error of the unoperated-on eye were corrected with a spectacle lens, then only in higher hyperopias would there be a chance of equalizing the sizes of the images in the two eyes.

5. The reader is left to estimate the aniseikonia in the many possible permutations and combinations of refractive errors in cases of anisometropia and also to estimate whether the separate ametropias are axial or refractive in origin.

Figure 2 shows those combinations of axial and refractive ametropias in the two eyes for which one could obtain images of the same magnification or size in the two eyes. In this figure the abscissa corresponds to the refractive power of the unoperated-on (phakic) eye and the ordinate corresponds to the basic refractive error of the operated-on (aphakic) eye prior to operation. Thus, whether or not the magnifications of the images in the two eyes are approximately balanced by the use of the contact lens will depend to a marked extent on the basic degree and origin of the ametropia prior to the operation.

Whenever unilateral aphakia is corrected with contact lenses, the problem of providing comfortable binocular vision for reading and near work is also an important one. As a general rule, if the unoperated-on eye

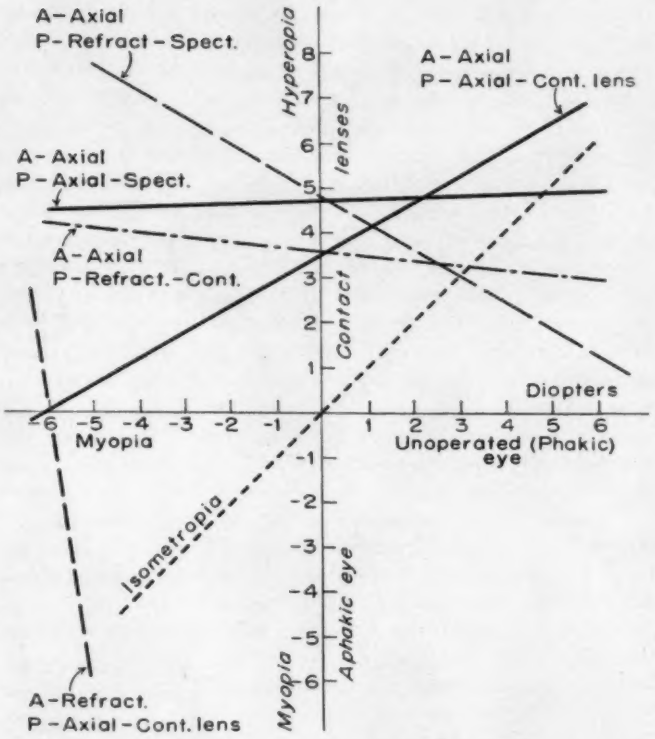

Fig. 2.—Combinations of refractive errors of the aphakic eye before operation, corrected by a contact lens, and of the phakic eye, corrected by either a spectacle or a contact lens, in which the magnifications of the images in the two eyes will be approximately equalized.

has adequate accommodation it is possible to make an additional correction of about +2.50 D. to the aphakic eye and add a 4% or 5% over-all afocal magnifying lens for the other eye, both in a spectacle frame. Of course, when the unoperated-on eye is presbyopic more nearly the same add for each eye can be given in spectacle lenses, thus minimizing the image magnification difference.

Physiologic Considerations

The foregoing discussion, based on the optics involved, has shown that, even when the unilateral aphakia is corrected with contact lenses, it is rarely possible to eliminate a residual aniseikonia. In general, differences in retinal image sizes greater than 9% will probably be present.

This question must then be answered: How do those patients who, according to the literature, are so corrected and who report comfortable binocular vision cope with a difference in retinal image sizes of this amount? One must recall that the threshold for the discrimination of retinal image size differences, under test conditions, is of the order of 0.25% to 0.5%, provided the visual acuity in the two eyes is 20/20 or better. As the visual acuity decreases, this threshold increases. Now, we are generally accustomed to consider any error of three to four times the threshold as significant and sufficient to cause some disturbance in binocular vision. Furthermore, clinical experience has shown that an aniseikonia of 5% to 6% is rarely found in patients who have normal binocular vision and that, if this amount of error does exist, the patient usually cannot wear the spectacles with the full refractive correction. Only by giving a partial refractive correction, that is, by making the image in one or both eyes slightly blurred, to reduce visual acuity, can

the patient wear the spectacles. This inability of patients to tolerate full large astigmatic corrections is well known.

It is also well known that even when a large difference in the sizes between the images of the two eyes exists or is produced artificially [15] fusion of images of small objects near the point of fixation is possible. This is true by virtue of the size of Panum's fusional areas in the macular regions compared with the disparity between the images in the two eyes produced by the aniseikonia. When a large difference in magnification exists, it has been shown that the entire region of binocular single vision is effectively turned about a vertical axis through the point of fixation. Objects lying near the fixation point always remain in this region.[30] Thus, the Worth four-dot test would be expected to show fusion and the Hering drop test or other tests for stereopsis to show the presence of stereopsis if the patient has binocular fixation, because the images of these test targets, as ordinarily used, would fall well within the macular areas. Outside the macular areas, however, the disparities between the images caused by the difference in magnification would increase rapidly toward the peripheral field. Even an 8% difference in magnification between the retinal images would cause a disparity between the images of a point lying 10 arc degrees peripherally from the fovea of 1.4△ (48 minutes of arc, or 0.8 arc degree). The size of Panum's area at this peripheral angle of 10 degrees would be only of the order of 20 minutes of arc or 0.6△. The images of all object points lying at peripheral angles greater than about 4 arc degrees in the frontoparallel plane would be outside Panum's areas and thus would tend to be seen double for all differences in magnification of the retinal images of the two eyes greater than 3%. Thus, a confusion of the images in all extramacular images near the fixation point would result.

It is well known that the images of peripherally located objects generally play an important role in binocular fusional movements.[6,30,40,41] Broenstrup has reported a restriction of the 5/1000 and 10/1000 isopters in the visual field of the uncorrected aphakic eye as compared with the fellow phakic eye, and Comberg could show by means of a specially designed test for the function of the retinal periphery that this function was considerably depressed in the uncorrected aphakic eye in respect to the phakic fellow eye. Both felt, however, that the aphakic eye contributed in some measure to the total act of vision of the patient. Ellerbrock has also shown that the vertical prism vergences are decreased when aniseikonia is artificially produced.

In trying to understand how the patients whose unilateral aphakia is corrected with contact lenses and who undoubtedly have a significant residual aniseikonia, and yet who report comfortable binocular vision, cope with the resulting difference in sizes of the retinal images, we must know (more precisely) something about the following:

(1) How well developed was the fusional ability when both eyes were used before the formation of the cataract. Studies should be made employing a means for measuring fusional movements of the eyes from peripheral stimuli.[6] The fusional responses to central and peripheral retinal areas should also be compared.

(2) To what extent had the patient learned suppression, particularly suppression of the peripheral images of one eye, following the cataract formation.

(3) The visual acuity of the two eyes and, particularly, how well a high visual acuity is maintained as the wearing of contact lenses is continued. The reduction of visual acuity in one or both eyes does reduce the discrimination of the confusion of the images and would permit a greater tolerance to aniseikonic errors. In this connection it is of interest to note that, among the 18 patients reported by Hirtenstein, of the 16 in whom the correction of unilateral aphakia with contact lenses was considered successful, 13 had 6/9 visual acuity or poorer in one eye or both. Similarly, of Schlosshardt's

nine patients who wore the contact lens with comfort and obtained stereopsis, seven had visual acuities of 4/5 to 4/8. Also, 16 of Györffy's 25 patients had visual acuities of 5/6 to 5/15. Sufficient data on the visual acuities were not given in most of the papers reporting successful use of contact lenses.

(4) To what extent is the patient satisfied with a confused peripheral vision.

(5) Finally, we need to have studies made with such patients on an apparatus of the type used for determinations of the horopter.

The question is frequently raised as to whether there cannot be a physiologic or functional realignment or adaptation of corresponding points which will fully compensate for the inequality of the magnifications of the retinal images. Certainly no such compensation is found when the unilateral aphakia is corrected with spectacle lenses. The difference to be compensated for is far too large. The evidence we have, as of now, suggests that as a general rule the organization of corresponding retinal elements is a stable one. Perhaps in young persons small aniseikonic errors are compensated for, but even in these cases compensation is probably not usually the rule.

Selected Cases

The following four cases have been selected as illustrating the optical principles described in the foregoing pages. The histories in these cases were obtained from the files of the late Dartmouth Eye Institute. While the contact lenses used were of the older type, the same general optical principles hold as for the newer types.

CASE 1.—The following example illustrates very well the fact that, if there was little or no refractive error in the two eyes prior to the formation of the cataract in one eye, it is difficult to avoid a residual aniseikonia even when the unilateral aphakia is corrected with contact lenses.

An 18-year-old youth experienced a perforating injury to the left eye, with a resultant aphakia in that eye, following a spontaneous absorption of the crystalline lens. The refractive error finally became R. E., $+0.50\bigcirc -0.50\times 180$, V. A.=20/15−; L. E., $+13.00\bigcirc -3.00\times 10$, V. A.=20/25. With trial-case lenses according to this prescription, in the direct-comparison type of eikonometer, the measured difference in magnification between the two eyes was 25% over-all combined with about 4% meridional at axis 90.

Contact lenses for both eyes were specified with the following dimensions:

	Radius of Front Curve, Mm.	Thickness, Mm.	Radius of Back Curve, Mm.
Right eye	8.0	1.5	7.5
Left eye	6.6	1.0	8.0

With the contact lenses as finished, the residual refractive error was R. E., $-0.50\bigcirc -0.25\times 90$, V. A.=20/15; L. E., $+2.00\bigcirc -1.50\times 90$, V. A.=20/40.

When these refractive errors were corrected with trial-case lenses, it was found that the aniseikonia was about 8%. That is, the magnification of the right eye had to be made larger by 8% in order to equalize the magnifications of the images in the two eyes.

Calculation shows that the shape-factor part of the total magnifications of the contact lenses for the two eyes was about 9% and 8% for the right and left eyes, respectively. With this selection of dimensions for the contact lenses, little was gained toward eliminating the residual aniseikonia. Inspection of Figure 1, assuming nearly equal and negligible original refractive errors in the two eyes, shows that a 9% to 10% difference might be expected, which is of the order of that found on the eikonometer.

CASE 2.—The following example is an interesting one in that the correction of both eyes with contact lenses for a unilateral aphakia resulted in high visual acuity and an unexplained low residual aniseikonia. The patient was a 13-year-old boy who was accidentally hit in the left eye by a BB shot from a playmate's air rifle. The removal of the crystalline lens from that eye was necessary. The refractive error then became

R. E., +0.75 sph, V. A.=20/20; L. E., +13.00⌒−4.00×80, V. A.=20/20.

Because of a large exophoria, which at times appeared as an exotropia, a total of 10$^{\Delta}$ base-in prisms was necessary before the patient could gain fusion. Measurements on the eikonometer (direct comparison type) with the above prescription in trial-case lenses showed that the image in the right eye had to be magnified by 25% over-all and a 4% meridional ×180 in order to make the magnifications of the images of the two eyes the same.

Zeiss-type contact lenses of the Dallos form were ordered according to the following dimensions:

	Radius of Front Curve, Mm.	Thickness, Mm.	Radius of Back Curve, Mm.
Right eye	7.95	0.5	8.0
Left eye	7.05	1.0	8.5

While the record of the refractive errors of the two eyes before the accident was not available, they must have been low, perhaps of the order of +0.75 D. An inspection of Figure 1 would show that, with ordinary contact lenses before both eyes, we would expect a residual aniseikonia of about 8% to 9%. The dimensions of the contact lenses given above were specified to keep this residual difference as low as possible, but there was little chance (theoretically) of eliminating it entirely.

Nevertheless, when these contact lenses were first worn, an uncorrected myopic error of about −1.00 D. was found in both eyes. With this correction in trial-case lenses, each eye had a visual acuity of 20/20. With prisms base-in necessary to correct part of the exophoria, the eikonometer test showed the magnifications of the images to be within 2% of being equalized. There was stereopsis, although when first tested with use of the Keystone DB6 card this was only 20% stereopsis. The curves of the contact lenses were subsequently altered to eliminate the remaining myopic error.

The patient was able to wear these contact lenses for four to six hours at a time without discomfort. He wore them in all his activities, at school, at camp, and even while swimming. The exotropia was later reduced surgically. This patient was followed for about two years, when he broke one of the contact lenses, at about which time a secondary cataract was noted to be developing.

Although from a clinical and practical point of view this case represents one of considerable success, from a theoretical point of view it is not entirely satisfactory. In the first place, it is not clear whether the residual aniseikonia that was to be expected really had been eliminated by the wearing of the contact lenses. The patient's sensitivity on the eikonometer was low. The exotropia that was present from the beginning and the failure to show high stereoscopic acuity suggested a basically imperfect binocular vision or, what was more probable, that the retinal images were blurred. There was clinical evidence that the boy could easily accommodate voluntarily with a concomitant reduction of the exotropia but with resultant blurred images. Hence a critical evaluation of the evidence fails to show that this case is one in which the correction of unilateral aphakia has restored normal efficient binocular vision.

CASE 3.—The following example does illustrate the successful use of contact lenses to correct unilateral aphakia. The patient was a 33-year-old man in whom a unilateral cataract developed in the left eye only following iritis. The patient stated that he had always been more myopic in the right eye than in the left. The manifest refractive error postoperatively was R. E., −6.00⌒−0.75×15; L. E., +10.00 sph. Visual acuity with this correction was 20/20 in each eye. With trial-case lenses to correct these refractive errors, the patient could fuse small parts of a line of letters on the wall chart if he looked intently at the part, but he reported that all other objects appeared double. The eikonometer measurement with use of trial-case lenses showed that the magnification (size) of the image of the right eye needed to be increased 34%

over-all in order to eliminate the aniseikonia. This measurement was obtained by the direct-comparison eikonometer and appeared higher than would have been expected.

Contact lenses of the Dallos form of blown glass and manufactured by the Zeiss Optical Company were prescribed for the two eyes, according to the following specifications:

	Radius of Front Curve, Mm.	Thickness, Mm.	Radius of Back Curve, Mm.
Right eye	8.53	0.5	7.50
Left eye	6.85	0.9	7.50

The particular curves for these contact lenses were calculated so as to reduce the aniseikonia due to the shape factor of the correction of the aphakia of the left eye. With these contact lenses on the eyes, the patient maintained binocular fixation and fusion and exhibited normal fusional movements and prism vergences. The eikonometer showed a residual aniseikonia requiring a correction before the right eye of about 1% to 2% over-all. The patient was able to wear the lenses for about six to seven hours a day but was troubled somewhat by cloudiness after about four hours. He noted an increased sensitivity to light.

Using the graph (Fig. 1), we can account for the balanced image magnifications by assuming that all the myopia of the unoperated-on eye was due to an axial ametropia and that the normal refractive error of the aphakic eye prior to operation was of the order of −2 D. myopia of mixed axial and refractive ametropia.

For reading, spectacles were prescribed as follows: R.E., 4% over-all afocal magnifying lens; L.E., +2.50 D. sph. With these, the patient was able to read for considerable lengths of time. The patient continued to use the contact lenses with comfort for nearly a year. After that time chalky deposits appeared on the lenses, and when the surfaces were repolished subsequently the curvatures of the lenses were altered. There was no further information regarding this patient.

Apart from the relatively short time this patient actually wore the contact lenses, the case illustrates the successful use of contact lenses for the correction of unilateral aphakia; however, contact lenses were required on both eyes. The secret of the success in this case is the relatively high axial myopia in the unoperated-on eye.

CASE 4.—This example is of some interest. The patient was a 57-year-old lawyer in whom, following an accident, the crystalline lens of the left eye was absorbed, leaving that eye aphakic. Although the structure of the vitreous body had also been somewhat altered by the accident, so that the vitreous was not clear, the visual acuity with correction was sufficient to warrant trying contact lenses. However, because of a tumorous formation on the upper part of the episclera, it was impossible to fit a contact lens that would be satisfactory. Air bubbles would form beneath the lens regardless of the size of the scleral portion of the lens used. In order to find a solution to the problem of the usual difference in magnification of the images when the aphakia was corrected with spectacle lenses, it was decided to put a contact lens over the nonaphakic right eye only, with such optical dimensions as would render that eye about as hyperopic as was the aphakic eye. The dimensions specified for that contact lens were as follows: radius of front curve, 10.5 mm.; thickness, 0.6 mm., and radius of back curve, 8.5 mm.

With the finished contact lens before the right eye, the refractive errors were R.E., +13.50 D. sph; L.E., +13.50 sph⌒−4.00 cyl×25. With this correction in trial-case lenses in the eikonometer, measurements showed that the magnification of the right eye should be increased about 3.5%. Aniseikonic spectacle lenses were designed to correct these refractive errors and to eliminate all but about 1.5% of the aniseikonia. Reading additions of +2.00 D., O. U., were also provided.

With the contact lens before the right eye and with these spectacles, the patient had seemingly excellent binocular vision. There

was stereoscopic acuity of 70% as measured on the Keystone DB6 card, a result which was normal for the reduced visual acuity of the two eyes. There was, of course, the unavoidable but nevertheless objectionable distortion from the lenses, inherent in most lens corrections for such high hyperopia, and a concomitant restriction of the field, which the patient found irritating. He experienced difficulty in walking while wearing the lenses because of the apparent nearness and inclination of the ground. Vibrations of the spectacles caused rapid apparent large movements of the visual field, because of the magnification, which "hurt" his eyes. Thus, one cannot say that the result in this case was a particularly successful one from the patient's point of view.

Conclusions

It is not the purpose of this paper to discourage the use of contact lenses in the correction of unilateral aphakia. The practical value of this form of correction would seem to be well attested by the papers dealing with it. Its use would be justified even if the criterion of success, from a clinical point of view, were simply the subjective benefit derived by the patient from wearing a contact lens correction. But this subjective criterion is not the only one that may be used, and favorable reports do not necessarily imply a cure. In this field as in others, for example in the field of ocular motility, the points of view of ophthalmologists vary greatly as to what constitutes a cure. So much depends on one's level of satisfaction. The purpose of this paper is to help in setting the sights as to the criteria of cure a little higher, to recall the optical and physiologic problems which exist with the correction of unilateral aphakia, and to point to further ways of investigating such patients to obtain a clearer insight into their binocular act. This, in turn, may lead to new approaches to the problem. One such new approach, the use of intraocular acrylic prostheses to replace the extracted lens, has actually been attempted by Rougier, who reported on a series of 18 cases of unilateral cataracts operated on by the Ridley method. He has found the results with regard to the achievement of binocular vision to be superior to those achieved in his 36 cases of contact lens correction. Rougier considers that the Ridley lens would offer the ideal solution to the whole problem if it were not for the limitations of this type of operation. These limitations make the use of contact lenses still indispensable in the correction of unilateral aphakia.

Summary

General optical considerations show that it may be difficult or impossible to reduce or eliminate the substantial amount of aniseikonia (9%) that remains after a unilateral aphakia is corrected by contact lenses. The ametropia that existed prior to the operation and the origin of that ametropia, whether axial or refractive, play important roles in determining the degree of aniseikonia. The magnification of the retinal image of the aphakic eye when corrected with a contact lens is much greater if the eye was originally axially myopic; it is less if originally the eye was axially hyperopic. The cases of unilateral aphakia in which the unoperated-on eye was axially myopic by about 6 D. and in which both eyes were corrected by contact lenses present a greater possibility of approximating or equalizing the magnifications of the retinal images in the two eyes. Similarly, those cases in which the eyes were axially hyperopic by at least 5 D., prior to operation, also present a better possibility if the aphakic eye is corrected by a contact lens and the unoperated-on eye, by a spectacle lens.

The general physiologic problem of how those patients who were reported in the literature as being able to wear contact lenses with restoration of binocular vision coped with the residual aniseikonia, as well as that information which must be obtained to help in answering that problem, is discussed.

Four selected case reports are presented as examples of the optical principles discussed in this paper, with emphasis on the difficulties involved.

Mayo Clinic.

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The Cataract Wound

Its Making and Closure

HUMBERTO ESCAPINI, M.D., Sc.D., F.A.C.S., F.I.C.S., San Salvador, El Salvador

For years ophthalmologists have endeavored to find out safe procedures for cataract surgery. The successful results actually obtained with the techniques in use must be gratifying to all those who, in the past and present, have contributed to their achievement.

The use of keratome and scissors in making the incision, the introduction of corneoscleral sutures, intracapsular extraction, and peripheral iridectomy have marked the main steps in the progress of cataract surgery.

I divide a cataract operation into several stages: (*a*) calming the patient and local or general anesthesia, (*b*) the making and closing of the incision, (*c*) total or peripheral iridectomy, (*d*) the extraction of the cataract (intra- or extracapsular, forceps or vacuum), and (*e*) postoperative care.

Without minimizing the importance of the different stages, such as having a quiet patient and a good local anesthesia, one may say that the most important one is the making and closing of the wound.

It does not matter if one performs an extracapsular extraction or a complete iridectomy, or if vitreous is lost, if one has a well-made incision and properly placed sutures; the results can still be good.

Technique

The incision has to be perfect. It is the clue to a successful operation. This has to be stressed to the utmost.

The incision ought to fulfill several requirements: A. Size. It should be 180 degrees or more. Smaller incisions make the extraction difficult when the cataract is grasped below and tumbled. When the cataract is grasped above, the incision can be smaller. B. Placement. It has to be made exactly at the limbus, behind the insertion of the conjunctiva. If it is placed on the scleral side one is apt to get much bleeding. C. The cut. It has to be perpendicular to the surface. The less beveled the incision is, the less are the chances for the corneal flap to slip off and the better the healing.

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Once the eye is fixed in the proper position, with a bridle suture passed under the superior rectus, the making of the incision should go through the following steps.

1. Conjunctival incision (Fig. 1). The conjunctiva should be cut right at its insertion, without disturbing the subconjunctival tissue, to avoid unnecessary operative and postoperative bleeding. It can be smaller than the corneal wound.

2. Making the groove at the limbus (Fig. 2). Once the conjunctiva is cut at its insertion, it withdraws, exposing the limbus. With a flamed probe, I cauterize any bleeding vessels and also the limbus at the site of the incision to avoid bleeding. With a very sharp knife, I make a partially penetrating incision at the limbus from 9 to 3 o'clock, cutting perpendicularly into the surface, and only the superficial two-thirds of its thickness. Much care should be exerted so as not to perforate.

3. Placing the sutures (Fig. 3). Sharp Grieshaber needles and 000000 mild chromic absorbable surgical (gut) sutures are used. Three sutures are placed, at 10, 12, and 2 o'clock. As the corneal lip of the wound is grasped with Castroviejo's corneal forceps,

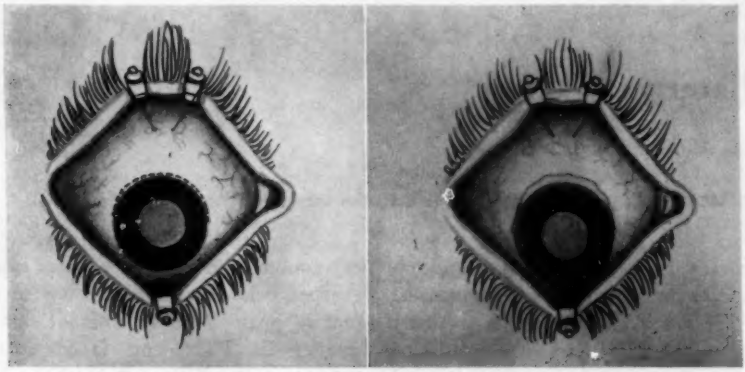


Fig. 1.—This drawing shows the site of the conjunctival incision and, with the conjunctiva withdrawn, shows the limbus, where the incision should be placed.

the needle is inserted, making a corneal bite of 1.5 mm. It has to come out at the bottom of the groove, and, without pulling it out, a similar bite is made on the scleral lip of the wound.

It is absolutely necessary that there be the most perfect apposition of the lips of the wound. The bite in each lip should be exactly alike in thickness and exactly on the same meridian to avoid any buckling, with the subsequent danger of leakage and delayed restoration of the anterior chamber or iris prolapse.

The sutures are now picked up in the groove with one of the needles of the sutures, pulled out, and laid aside (Fig. 4). Gut is always more difficult to handle than silk; to make handling it easier, it always has to be kept wet.

4. Completing the wound (Fig. 5). With a sharp knife the anterior chamber is opened at one of the ends of the groove, preferably the temporal end, because from here the incision is more easily enlarged. The opening has to be large enough to introduce one of the blades of the scissors. With the Castroviejo cataract scissors, the incision is finished, with the blades being kept perpendicular to the surface. The sutures are retracted by pulling on each of their ends with forceps, one held by the surgeon and the other by the assistant.

Fig. 2.—The groove at the limbus is made with a very sharp knife. It must be at least one-half of the circumference of the limbus, cut two-thirds of its thickness, and perpendicular to the surface.

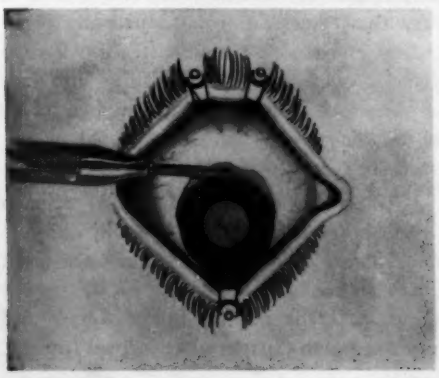
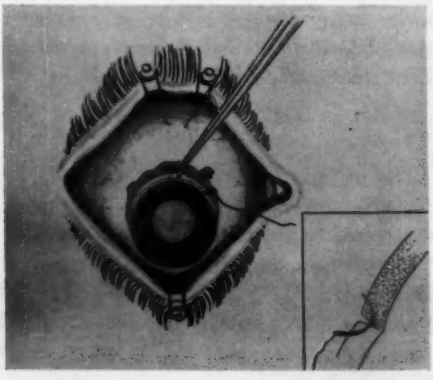


Fig. 3.—Once the limbic groove is made, three 000000 gut sutures are placed. The bite of the needle should be of the same depth on both lips of the wound and be exactly on the same meridian.



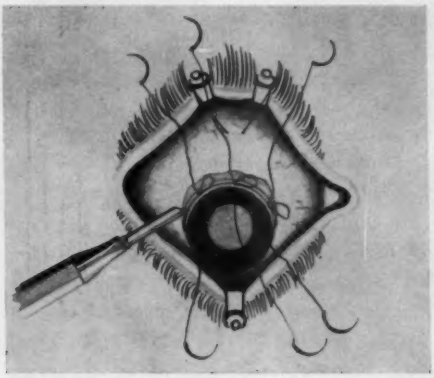


Fig. 4.—The threads are pulled out from the bottom of the groove and laid away. The anterior chamber is opened on the temporal end of the incision with a knife.

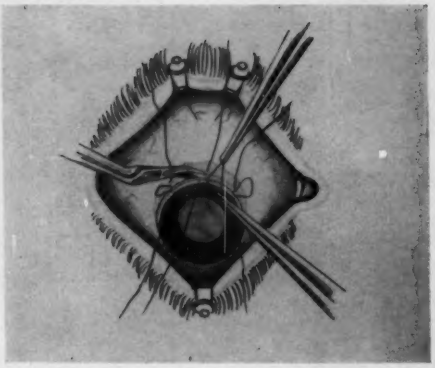


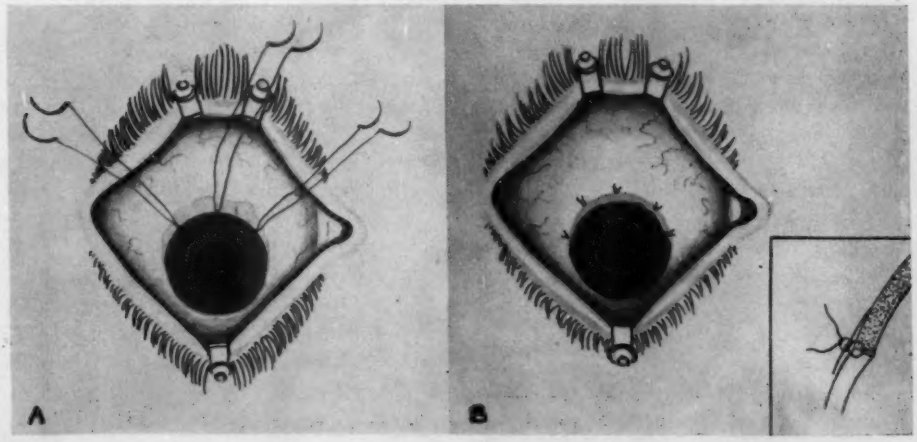
Fig. 5.—The incision is finished with Castroviejo's cataract scissors, while the sutures are pulled away to avoid cutting them. The blades of the scissors should be kept perpendicular to the surface.

5. Closing the incision (Fig. 6). Once the cataract is extracted, the sutures are pulled and tied, tight enough to bring the lips of the wound into close apposition. After the iris is repositioned, the conjunctiva is pulled down and the two needles of each suture are passed through it, 2 mm. from the edge and 1 mm. apart. When tied again, they fix the conjunctiva over the incision. Another conjunctival suture is placed at each end of the incision. In this way the whole incision is covered by the conjunctiva.

Comment

The technique herein described has three very important features: A. The incision perpendicular to the surface of the cornea guarantees a better apposition of the lips of the wound and prevents slipping of the cut surfaces, with the subsequent danger of a leaking wound. As shown in Figure 7, a beveled cut in a sphere allows easy slipping of its surfaces. On the other hand, if a perpendicular cut is made its surfaces fit much better and this averts displacements.

Fig. 6.—*A*, after the cataract is extracted, the sutures are tightened and tied, just enough to bring the lips of the wound into close apposition. *B*, the needles are then passed through the conjunctiva 2 mm. above the cut edge, 1 mm. apart, and are tied again.



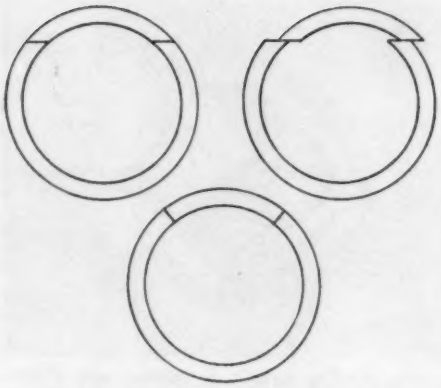


Fig. 7.—This drawing shows how a slanting cut in a sphere allows slipping of the cut surfaces; on the other hand, the edges of a perpendicular cut remain a perfect fit.

B. Three corneoscleral sutures, perfectly appositional and holding the same bite in each lip of the wound, give a watertight closure and add considerable safety to the operation. The use of gut sutures spares psychological and material trauma to the patient. It does not increase the postoperative reaction to the point of being deleterious. C. The conjunctival flap, being fastened to the wound, protects it from infection and the growing in of the corneal epithelium.

I have used this technique for the last year and have performed 170 extractions in 118 patients. Previously I had used different techniques, but occasional iris hernia observed kept me searching for a safer one.

In five cases there was hyphema, which absorbed without affecting the final outcome. I am convinced that the hemorrhages happened when the wound was placed on the scleral side of the limbus. It should be as much anterior as possible.

Flattening of the anterior chamber, with or without choroidal detachment, observed in 30 cases, was the commonest postoperative complication. With the use of acetazolamide (Diamox) it was rapidly controlled.

In none of the cases in this group was there iris prolapse. The wound was so well closed that it withstood trauma in careless patients during the immediate postoperative period.

Whenever there was vitreous in the anterior chamber at the end of the operation, the wound healed as well as in the normal cases. However, there was always more postoperative congestion which lasted longer.

In most of the cases there was a rather small astigmatism that ranged from 0 to 1 D.

It is obvious to every eye surgeon that the wound in cataract surgery plays the most important role in the final outcome of the operation. With a properly made and well-closed wound, one can still have good results in spite of loss of vitreous, extracapsular extraction, severe postoperative hemorrhage, and trauma to the eye.

With the results reported above, I consider the technique here described as the safest one I have ever used. To carry it out properly, a very sharp knife and good Grieshaber needles are absolutely necessary.

Summary

A technique for the cataract incision is described. The incision should be placed at the limbus, involve its upper one-half, and be perpendicular to the surface.

Before the anterior chamber is opened, a groove two-thirds of the limbus thickness is made and three perfectly appositional 000000 absorbable surgical (gut) sutures are placed, with use of Grieshaber needles.

The anterior chamber is opened at the temporal end of the groove, and the incision is completed with Castroviejo's cataract scissors. The conjunctiva, cut at the limbus in the beginning of the operation, is pulled down; the sutures are passed through it 3 mm. from the cut edge and in this way are anchored to the wound.

This technique has been used for the last year in 170 eyes. The commonest complication encountered has been flattening of the anterior chamber, with or without choroidal detachment.

3a. Calle Poniente No. 43.

Effect of Different Steroids on the Healing of Nonperforating Corneal Wounds in Rabbits

P. K. BASU, M.B., D.O.M.S., San Francisco

Because of the reports of the inhibitory action of corticosteroids on wound healing, many eye surgeons have hesitated to use them during the immediate postoperative period and have been reluctant to perform corneal surgery on patients who are under steroid therapy. Others, however, are of the opinion that steroids do not prevent corneal healing when used within the therapeutic dosage.

In histologic studies, Ashton and Cook [1] observed inhibition of healing in perforating corneal lesions in rabbits treated with a high dose of cortisone subconjunctivally. Newell and Dixon [2] studied the healing process of penetrating corneal grafts in rabbits both clinically and microscopically and found that cortisone given subconjunctivally delayed wound healing through failure of fibroblastic proliferation. By testing the tensile strength of the incisions and by histological sections, Palmerton [3] showed that topically administered cortisone caused inhibition of healing of penetrating corneal wounds in rabbits. McDonald and coworkers [4] reported poor healing of perforating corneal wounds in rabbits following subconjunctival hydrocortisone therapy. Rossi [5] also reported delayed healing of corneal wounds with prednisone.

On the other hand, Ashton [6] found that with therapeutic dosages of cortisone given subconjunctivally there was no inhibition of healing of perforating corneal lesions in rabbits. More recently, in experiments similar to those of Palmerton,[3] Fink and Baras [7] could show no significant effect on the tensile strength of the scar in experimentally induced corneal wounds by using intramuscularly administered cortisone.

There are no reports in the literature on the action of prednisolone on the healing of corneal wounds.

The present study was devised to compare the actions of the different steroids in concentrations recommended for human therapeutic use [8-10] on standard nonperforating corneal lesions in rabbits. The results in each series of lesions treated by one of the steroids were compared with those for groups receiving a placebo or no medication.

Methods and Materials

Ninety-six albino rabbits of approximately the same age and weight were used. They were kept in the same environment and had the same type of food. All the experiments were completed within a period of six weeks.

One central and one peripheral nonperforating thermal burn were produced by cauterization with a "Hyfrecator" in each eye of an experimental animal. An identical amount of current and voltage was used, and the electrode was placed on the cornea with the same amount of pressure for a given length of time in each case.

The central lesion was made within an area of 5 mm. in diameter in front of the pupil. The center of the peripheral lesion was placed 2 mm. from the limbus at the meridian of the superior rectus muscle. The diameter of all the lesions was 1 mm., and the wound involved the superficial two-thirds of the cornea. The operation was done with use of local anesthesia, obtained with 1 drop of 1% tetracaine (Pontocaine) solution.

Medication, started on the day of operation, was of three types: (1) an ointment placebo, (2) a

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TABLE 1.—*Design of the Experiments*

Group	Sub-group	Animals, No.	Medication R. E.	Medication L. E.
I		12	Nil	Nil
II		4	Nil	Placebo
III	A	3	Cortisone oint.	Placebo
	B	3	Hydrocortisone oint.	Placebo
	C	3	Prednisone oint.	Placebo
	D	3	Prednisolone oint.	Placebo
IV	A	2	Cortisone inj.	Placebo
	B	2	Hydrocortisone inj.	Placebo
	C	2	Prednisolone inj.	Placebo
V	A	2	Cortisone oint.	Cortisone oint.
	B	2	Hydrocortisone oint.	Hydrocortisone oint.
	C	2	Prednisone oint.	Prednisone oint.
	D	2	Prednisolone oint.	Prednisolone oint.
VI	A	2	Cortisone inj.	Cortisone inj.
	B	2	Hydrocortisone inj.	Hydrocortisone inj.
	C	2	Prednisolone inj.	Prednisolone inj.
VII	A	2	Cortisone oint.	Cortisone inj.
	B	2	Hydrocortisone oint.	Hydrocortisone inj.
	C	2	Prednisolone oint.	Prednisolone inj.
VIII	A	5	Cortisone oint.	Hydrocortisone oint.
	B	5	Cortisone oint.	Prednisone oint.
	C	5	Cortisone oint.	Prednisolone oint.
	D	5	Hydrocortisone oint.	Prednisone oint.
	E	5	Hydrocortisone oint.	Prednisolone oint.
	F	5	Prednisone oint.	Prednisolone oint.
IX	A	3	Cortisone inj.	Hydrocortisone inj.
	B	3	Cortisone inj.	Prednisolone inj.
	C	3	Hydrocortisone inj.	Prednisolone inj.

steroid in ointment base, and (3) a steroid in aqueous suspension. The ointments were used topically, and the aqueous suspensions of the steroids were injected subconjunctivally or under Tenon's capsule.

Four steroid ointments, namely, cortisone acetate (1.5%), hydrocortisone acetate (1.5%), prednisone (0.5%), and prednisolone (0.5%) were applied twice a day in quantities sufficient to fill the upper fornices. For subconjunctival or sub-Tenon injection three steroids, namely, cortisone acetate (5 mg.), hydrocortisone acetate (5 mg.), and prednisolone (1.25 mg.) were used on alternate days, starting from the day of operation.

In a control group of animals no medication was given.

Neither antibiotics nor any other antiseptic drug was used during the postoperative period. The animals were killed at different intervals. The maximum period of observation was 15 days.

To provide an adequate comparison of the mode of wound healing in the treated and control animals, the series of 96 rabbits was divided into nine separate groups, as shown in Table 1.

TABLE 2.—*Day of Cessation of Fluorescein Staining of the Corneal Epithelium in Eighty per Cent of the Corneal Lesions*

Group	Lesion	Day of Cessation of Fluorescein Staining
Control	Central	5
	Peripheral	4
Placebo	Central	5
	Peripheral	4
Steroid ointments	Central	5
	Peripheral	4
Steroid injections	Central	5
	Peripheral	4

Each rabbit was examined daily with the slit lamp after the cornea was stained with fluorescein. The staining of the corneal epithelium, size and density of the corneal opacity, and vascularization of the lesion were carefully noted, and photographs were taken. It was found that in the recording of the corneal opacities retroillumination was very helpful. The size of the lesion was measured in fractions of millimeters. The blood vessels were counted numerically.

A total of 384 lesions were examined macroscopically, and 346 histological sections were studied. Each section was stained with hematoxylin and eosin and with Masson's stain.

Results and Observations

Macroscopic Observations.—The results for 80% of the lesions are presented in Tables 2, 3, and 4.

In Table 2 it will be seen that the healing of the corneal epithelium proceeded at the same rate in the treated and control animals, regardless of the form or mode of steroid treatment. Peripheral lesions healed one day in advance of the central lesions.

In Table 3 it may be seen that the diminution of the size of the lesion followed a gradual course and proceeded at the same

TABLE 3.—*Size of the Corneal Wounds in Eighty per Cent of the Corneal Lesions*
Summary of Groups I to IX

Group	Lesion	Size of Corneal Wound, Mm. Day 2	Day 8	Day 15
Control	Central	1.00	0.85	0.75
	Peripheral	1.00	0.75	0.50
Placebo	Central	1.00	0.85	0.75
	Peripheral	1.00	0.75	0.50
Steroid ointments	Central	1.00	0.85	0.75
	Peripheral	1.00	0.75	0.50
Steroid injections	Central	1.00	0.85	0.75
	Peripheral	1.00	0.75	0.50

Fig. 1.—Central corneal lesion. Type 1 opacity.

Fig. 2.—Central corneal lesion. Type 2 opacity.

rate in control, placebo, and all steroid-treated cases. Reduction of the size of the lesion occurred more rapidly in peripheral than in central wounds.

The density of the scar was divided into three types according to the degree of visibility of the iris structures through the floor of the lesion. In Type 1 the opacity was so dense that the pattern of the blood vessels of the iris was not visible through the lesion (Fig. 1). Type 2 opacity was such that the structures of the iris were just visible (Fig. 2). Type 3 opacity was thin enough for the iris structures to be seen fairly clearly (Fig. 3). The results are presented in Table 4.

In Table 4 it may be seen that the reduction of the opacity was uniform in all cases of both treated and untreated lesions. There was no difference in the rate of healing with different steroid preparations in any form. The reduction of the opacity in the peripheral lesions was faster than that in central lesions.

Vascularization did not develop in any central lesion, whereas 98% of the peripheral lesions were invaded with blood vessels. The numbers of the blood vessels were counted and classified into grades. Grade I represented a single large or 5 fine blood vessels, and Grade II, 2 large or 6 to 10 fine blood vessels. The vascularization of 75% of the peripheral lesions is presented in Table 5.

Fig. 3.—Central corneal lesion. Type 3 opacity.

In 75% of the treated and control peripheral lesions there was no difference in the mode of vascularization. The blood vessels began to appear after three days, became more intense after the first week, and began to recede during the third week.

TABLE 4.—*Types of Opacities of the Corneal Wounds in Eighty per Cent of Lesions*
Summary of Groups I to IX

Group	Lesion	Type of Opacity		
		Day 2	Day 8	Day 15
Control	Central	1	1	2
	Peripheral	1	2	3
Placebo	Central	1	1	2
	Peripheral	1	2	3
Steroid ointments	Central	1	1	2
	Peripheral	1	2	3
Steroid injections	Central	1	1	2
	Peripheral	1	2	3

TABLE 5.—*Grades of Vascularization in Seventy-Five per Cent of the Peripheral Lesions*
Summary of Groups I to IX

Group	Grade of Vascularization			
	Day 2	Day 5	Day 8	Day 15
Control	--	I	II	I
Placebo	--	I	II	I
Steroid ointments	--	I	II	I
Steroid injections	--	I	II	I

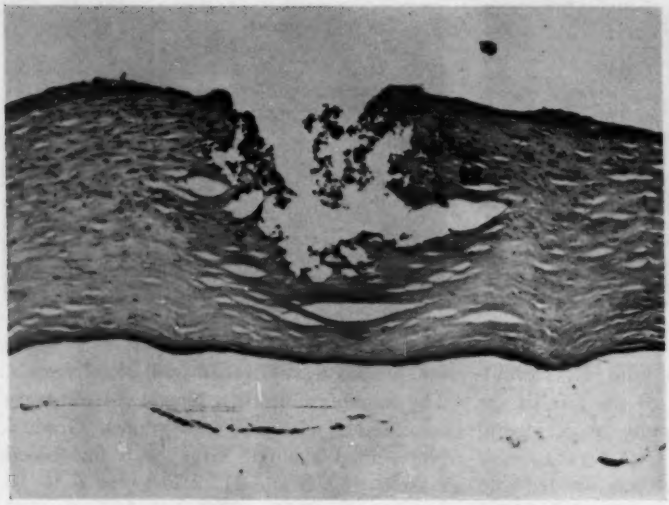

Fig. 4.—Histological picture of central corneal lesion on the first day.

Microscopic Observations.—Destruction of the tissue in the diathermized area was represented by a semilunar cavity occupying the superficial two-thirds of the cornea. The adjoining stroma, Descemet's membrane, and the endothelium appeared normal (Fig. 4).

In general, the progressive development in the healing process was well shown in all groups. The daily developments in the histological process of healing of corneal lesions were compared for periods up to 15 days in the control group and in the experimental groups treated with various steroids or a placebo. For this purpose a system of grading was developed based on the histological changes on the 4th, 6th, 10th, and 15th days. For the sake of convenience, the healing process in central lesions only is described according to this system of grading.

The earliest sign of healing was manifested after 24 hours by the proliferation of epithelial cells at the margins of the lesion.

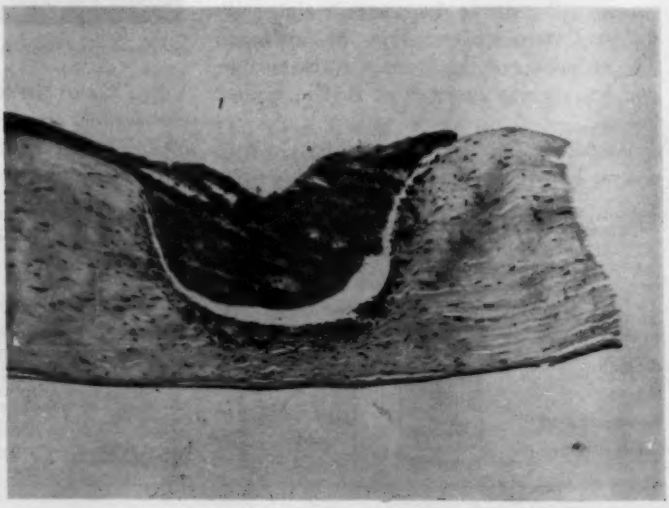

Fig. 5.—Histological picture of central corneal lesion on the fourth day. First stage of healing.

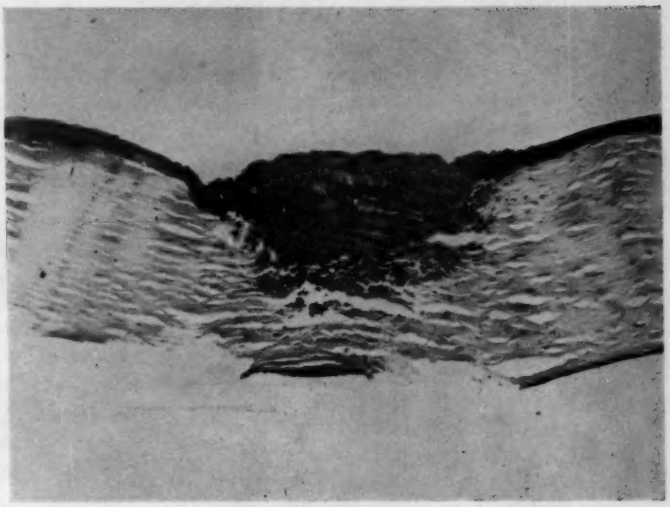

Fig. 6.—Histological picture of central corneal lesion on the sixth day. Second stage of healing.

By the fourth day most of the cavity of the lesion was filled with a thick epithelial plaque. A crescentic space remained between this epithelial cell mass and the stromal wall of the lesion. The tissue lining the cavity of the lesion became infiltrated with inflammatory cells, especially polymorphonuclear cells. This represented the first stage of healing (Fig. 5).

By the sixth day the condition of the epithelium remained the same but the space between the epithelial cell mass and the stroma disappeared, owing to the growth of fibroblasts. By the end of the first week these fibroblasts outnumbered all other inflammatory cells. This represented the second stage of healing (Fig. 6).

By the 10th day well-defined collagenous fibers could be seen, although their first appearance could be detected with Masson's stain one or two days earlier. Gradually the fibroblasts invaded the epithelial-cell mass from all directions, laying down collagenous fibers along their way. The

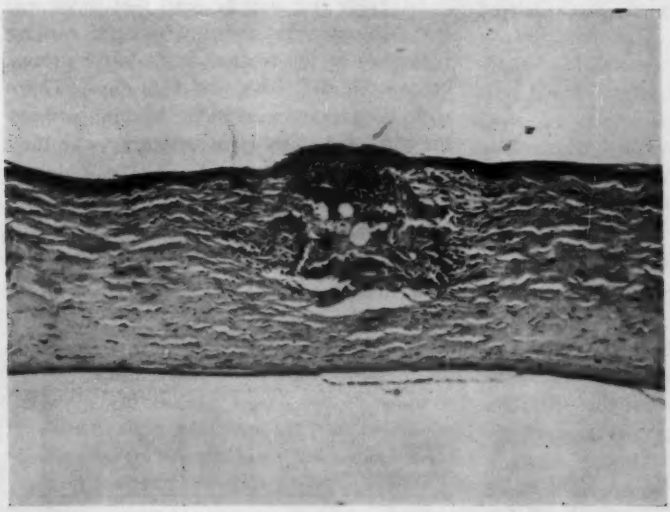

Fig. 7.—Histological picture of central corneal lesion on the 10th day. Third stage of healing.

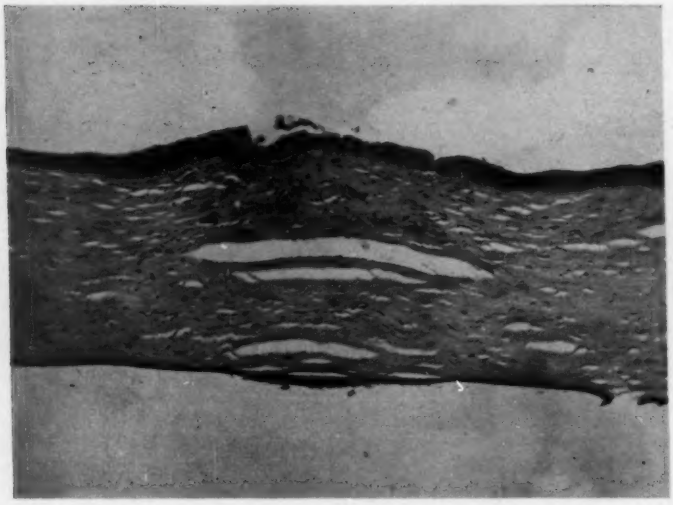

Fig. 8.—Histological picture of central corneal lesion on the 15th day. Fourth stage of healing.

epithelial-cell plaque became divided and subdivided into small islands and began to disappear from the stromal region. At first the long axes of the fibroblasts ran in different directions and the deposition of the collagenous material was also very irregular. The whole area of the lesion remained filled with a loose kind of tissue containing a few islands of epithelial cells. This represented the third stage of healing (Fig. 7).

By the 15th day the number of fibroblasts began to be reduced and they began to assume more parallel arrangements. The collagenous fibers were found to be arranged in layers parallel to the epithelial surface, but still the site of the lesion could be recognized by the accumulation of abnormal cells and by the stromal tissue which was less compact than the surrounding stroma. The epithelial layer was almost normal by this time. This represented the fourth stage of healing (Fig. 8).

A comparison of the healing process in peripheral and in central lesions showed certain differences. In the peripheral lesions the mode of healing of the epithelium and the stroma was similar to that seen in the central lesions except that all the processes were one or two days in advance of the same stage in the latter. Although inflammatory cells were of the same type in both lesions, they were more numerous in the peripheral lesions, especially on the limbal side. Vascularization did not occur in any central lesion, but almost all of the peripheral lesions were vascularized. The intensity of vascularization was most marked between the 7th and 10th days, after which the blood vessels began to recede.

In the assessment of the histological studies the central lesions and the peripheral lesions were considered separately, and the results of the study of the central lesions are shown in Table 6.

In Table 6 it will be seen that there was no difference in the microscopic healing processes in the treated and control groups on the 4th, 6th, 10th, and 15th days. There were no interferences in the healing between the different steroids in whatever way they were given.

Infection.—In no instance in these experiments was there any evidence of infection in any of the lesions.

TABLE 6.—*Microscopic Stages of Healing of the Central Corneal Lesions*
Summary of Groups I to IX

Group	Stage of Healing			
	Day 4	Day 6	Day 10	Day 15
Control	1	2	3	4
Placebo	1	2	3	4
Steroid ointments	1	2	3	4
Steroid injections	1	2	3	4

Comment

In previous studies of corneal wound healing in rabbits workers have used various kinds of standard lesions and different dosages of the steroids. For this reason, it is very difficult to compare results of one worker with that of another.

It is possible that the heading of nonperforating corneal wounds in rabbits may differ from that of perforating wounds. In this study the rate of healing was different in central and in peripheral wounds. To exclude the possibility of variability, nonperforating corneal wounds were used, because it was felt that the highly fibrinous secondary aqueous of rabbits might prevent consistent wound healing when interposed within the wound.[7]

The diathermy lesion was very uniform as far as measurements were concerned. The growth of the fibroblasts and collagenous fibers was well demonstrated in the area of the lesion, especially with connective tissue stains.

The more rapid rate of healing and vascularization and the greater infiltration of the peripheral lesions by inflammatory cells may be due to better nutrition of the lesions close to the limbus and to better protection offered by the upper lids.

In the over-all experiments there were no differences in the process of healing, as observed both clinically and histologically, in the groups treated with the different steroids, whether with ointments or by subconjunctival or sub-Tenon injections. The groups which received no medication or which received only the placebo showed a similar process of healing. When all the steroid-treated groups were compared with the control group, the rate and the type of healing were found to be the same in about 80% of the lesions, and thus there is no doubt that, under the experimental condition described, steroids did not inhibit corneal wound healing.

Ninety-eight per cent of the peripheral lesions were vascularized, but none of the central lesions showed any blood vessels. In 75% of the peripheral lesions there was no difference in the nature of vascularization when treated and untreated groups were compared. In the remaining 25% of the lesions it was difficult to draw any definite conclusion, though there was slight indication that the treated lesions were less vascularized than the untreated ones, and, of the steroids, cortisone showed more inhibitory action on blood vessels than did hydrocortisone, prednisone, and prednisolone.

Summary

The process of wound healing in nonperforating central and peripheral lesions in rabbits treated with different steroids was compared clinically and histologically with the healing process in a control series receiving no medication.

The progress and rate of healing in the treated and control lesions, either central or peripheral, were similar in 80% of the wounds.

The rate of healing of the peripheral lesions was faster than that of the central lesions in both treated and untreated groups.

Almost all the peripheral lesions were vascularized, and there was no evidence, at least in 75% of the lesions, that the steroids had any inhibitory action on the blood vessels.

There was no indication that the steroids predisposed the lesions to infections.

Dr. Michael J. Hogan, Director, Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco, gave comments and suggestions regarding the carrying out of this study.

Department of Ophthalmology, Banting Institute, 100 College St., Toronto, Canada.

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Death of Dr. William Zentmayer

Dr. William Zentmayer, one of the foremost figures in American ophthalmology, died at his home in Merion, Pa., on March 18, 1958. He was a member of the Editorial Board of the ARCHIVES OF OPHTHALMOLOGY from its beginning, in 1929, and remained active on the Board until his death, at the age of 93. The Editorial Board wishes to pay tribute to a great clinician whose counsel will be greatly missed. His obituary will appear in a forthcoming issue.

FRANCIS H. ADLER, M.D.
Chief Editor

Macular Edema, Papilledema, and Optic Atrophy After Cataract Extraction

ROBERT B. WELCH, M.D., and JACK C. COOPER, M.D., Baltimore

This paper deals with the entities of macular edema, papilledema, and optic atrophy which occasionally follow apparently uneventful cataract surgery.

This discussion may be prefaced by noting that papilledema in association with ocular hypotony is a well-established clinical entity. Such changes have been observed following perforation of the globe, trauma to the eye without perforation, prolonged inflammation, and, especially, fistulizing operations for glaucoma. The importance of decreased intraocular pressure in the pathogenesis of this lesion is well established by many clinicopathologic and experimental studies.[1] Brégeat[2] has pointed out that in addition to papilledema there may be extension of edema into the macula which, if persistent, may result in macular cyst formation and degeneration. Thus it is well established that a variety of insults which produce hypotony may also be accompanied by the production of macular edema.

Reports of papilledema and macular edema following cataract surgery, however, have been absent from the literature until recent years. In 1945 Hughes and Owens[3] reviewed 2086 cases of cataract extraction performed at the Wilmer Institute. In their analysis of complications there was no mention of macular or disc edema secondary either to hypotony or to any other cause. Dunnington,[4] in 1949, reported observations on late fistulization and hypotony as postoperative complications of ocular surgery. He noted that if hypotony persists edema of optic nerve and retina may appear.

Dellaporta,[5] in 1955, also reported fundus changes in hypotony. He presented cases with papilledema and macular edema in association with hypotony. This condition occurred in one case following an uneventful cataract extraction and in others after cyclodialysis for aphakic glaucoma. He suggested that the etiology was sudden hypotony caused by vitreous membrane rupture.

The importance of the integrity of the anterior hyaloid membrane of the vitreous has been emphasized by other authors. Hughes and Owens mentioned that rupture of the hyaloid face occurred in a number of patients several months after normal healing and was responsible for blurring of vision. Kirsch and Steinman,[6] in 1954, also reported on spontaneous rupture of the anterior hyaloid membrane following cataract surgery and noted that this occurrence had been previously considered innocuous. Among the complications listed was a permanent decrease in visual acuity of unexplained etiology, although no reference was made to macular edema or papilledema. At about this same time, Irvine[7] presented his "Newly Defined Vitreous Syndrome Following Cataract Surgery." The essence of this syndrome is the formation of vitreous adhesions to the wound following late rupture of the hyaloid face, with associated irritability of the eye, vitreous opacities, and reduction of vision as a result of macular changes. He felt that vitreous adhesions to the wound played a considerable role in the development of macular degeneration. Chandler[8] also has referred to the onset of macular difficulties developing after an uneventful cataract

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From the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital and University.

extraction in which the immediate visual result was a normal 20/20. He felt that subnormal tension and prolonged postoperative inflammation might be predisposing causes.

In 1954 and 1956 Nicholls [9,10] reported the concurrence of macular edema with cataract extraction. Some of his cases showed the onset of macular edema several months after cataract extraction, while in others the onset occurred soon after operation. Several of the cases were associated with prolapse forward of the vitreous. He suggested that the predisposing cause of this condition is a vascular instability in the retina and/or choroid in the macular region. Although at first Nicholls considered that anxiety played a prominent role, he has since deemphasized this.[11]

Having considered the occurrence of papilledema and macular edema following cataract extraction, we come to the consideration of optic atrophy. A cursory review of the literature reveals only one report of this condition following cataract extraction. Vila-Coro,[12] in Spain, reported 10 cases of optic atrophy in 5000 cataract extractions. He believed that optic atrophy secondary to papilledema could occur following cataract extraction as a result of vascular changes in the disc. He based his opinion upon the study by Sobanski [13] of arteriovenous pressure relationship.

In summary, papilledema, macular edema, and optic atrophy occurring after cataract extraction have not been fully appreciated. A number of possible reasons for failure of recognition of these conditions can be enumerated. First would be the rarity of occurrence. Second might be the transient nature of the edema. A third point, and one which should be emphasized, is the difficulty in recognizing macular edema. Finally would be the attributing of the clinical state to other causes, such as refractive changes, iridocyclitis, or macular degeneration purely on a senile basis.

We have attempted in this study to find cases of macular edema, papilledema, and optic atrophy which we thought could be related to cataract extraction. Our cases were obtained from a review of 1600 cases of cataract extraction from the ward service of the Wilmer Institute, from cases personally seen by us, and from cases seen by the private staff of the Wilmer Institute. There were 21 eyes in 18 cases. We have divided these eyes into four groups. Group I contains seven eyes with only macular edema or cystic degeneration. Group II contains nine eyes with macular edema and papilledema. We subdivided Group II into four eyes with predominance of macular edema, four eyes in which papilledema was outstanding, and one eye in which both features were prominent. In Group III are four eyes with only papilledema. Group IV consists of three eyes with optic atrophy.

Report of Cases

CASE 1.—A 70-year-old white man had B. P. 120/70 and mild arteriosclerosis. Emotional status was stable. General health was good. Chest x-ray showed fibrocalcific infiltration of left apex. The patient had had 10 years previously an attempted intracapsular cataract extraction, with resultant 20/30 vision. On March 20, 1956, a combined intracapsular cataract extraction was performed on the right eye. No vitreous was lost. Postoperative course was uneventful. On April 27, 1956, vision O. D. was 20/50—1. The vitreous face was broken, with strands in the anterior chamber. Tactile tension was normal. On May 22, 1956, vision O. D. was 20/100. A circumscribed lesion was seen above the macula. On June 6, 1956, examination with the Hruby lens revealed macular elevation with 6 to 10 cysts in the macula. On July 11, 1956, vision O. D. was 20/70. There was a 5-degree central scotoma to 1/1000 white and a 3-degree central scotoma to 3/1000 red and blue. Follow-up was for four months, when vision O. D. was 20/70 and the macula was elevated and had six or seven cysts.

CASE 2.—A 60-year-old white man had B. P. 120/65, good general health, and emotional stability. On May 27, 1946, he had an intracapsular cataract extraction on the left eye, without loss of vitreous. On June 26, 1946, vitreous bulged into the anterior chamber. Tactile tension was normal. Vision O. S. was 20/20. On Aug. 12, 1946, an intracapsular cataract extraction was performed on the right eye, without complication. On Sept. 18, 1946, vision O. U. was 20/20; the fundi

were normal. On Nov. 19, 1946, vision O. U. was 20/50 and macular edema was bilateral. The state of the vitreous was not noted. On Dec. 4, 1946, vision O. U. was 20/20—2. Follow-up was for two and one-half years, when vision O. U. was 20/15. Tension and fundi were normal.

CASE 3.—A 77-year-old white woman had B. P. 200/100, generalized arteriosclerosis, and emotional lability. She had on May 24, 1955, an uneventful intracapsular cataract extraction on the left eye. Redness of the eye persisted for seven weeks. On July 9, 1955, vision O. S. was 20/20. By July 17, 1955, she had visual decrease in the left eye and difficulty in reading. Vision O. S. was 20/40. On Dec. 14, 1955, vision O. S. was 20/30 with difficulty. The hyaloid membrane of the vitreous was intact. Macular reflex was abnormal, with striae. Central field showed a relative 3-degree central scotoma to white and an absolute central scotoma to color. On Sept. 28, 1956, vision O. S. was 20/400, with +11.00 sphere. The anterior chamber had normal depth. There were vitreous opacities, and the anterior hyaloid face was broken with a large hole. No vitreous strands appeared in the wound. There was a 5-degree central scotoma to 4/2000 white. Hruby lens examination revealed serous detachment of the macula similar to that seen in central serous retinopathy and was 2½ disc diameter in size. Tension was 18 mm. Hg (Schiøtz). On Nov. 5, 1956, an intracapsular cataract extraction was performed on the right eye. One month postoperatively the vitreous face was intact and vision O. D. was 20/25. Two months postoperatively the vitreous face was ruptured. Tension was normal, and vision was 20/40. The macula was normal to Hruby lens examination. Follow-up was for 19 months. Vision O. S. was 20/200, and macular edema persisted.

CASE 4.—A 69-year-old white man had B. P. 160/100, emotional stability, and good general health. On April 18, 1956, he had an attempted intracapsular cataract extraction on the right eye, without loss of vitreous. On April 25, 1956, an intracapsular cataract extraction was performed without complication on the left eye; the postoperative course remained uneventful. In June, 1956, vision O. U. was 20/15. Two months postoperatively the right eye became red, with decrease in vision to 20/40. Aqueous ray was positive. The patient was treated with topical cortisone for iritis. On Dec. 14, 1956, vision O. D. was 20/40, tension was 14 mm. Hg (Schiøtz). The pupil was eccentric above, and the vitreous face was broken, but vitreous was not in the wound. There were capsular remains above. The vitreous was semifluid. As seen with the Hruby lens, the right macula had two cysts and a small petechial hemorrhage. There was a central scotoma to 2/1000 red. Follow-up was for eight months, when vision O. D. was 20/40 and two macular cysts were seen.

CASE 5.—A 65-year-old white man had B. P. 140/70, with normal general physical examination. He was emotionally stable. On Feb. 24, 1955, an intracapsular cataract extraction was performed on the right eye. Operation was uneventful, with no loss of vitreous. Small hyphema was seen on the third postoperative day. The anterior chamber was normal on the ninth day. Two weeks postoperatively there was a flat chamber and a combined detachment, which disappeared in one week. In October, 1955, vision O. D. was 20/30. Vitreous floaters were present. On June 8, 1956, the patient complained of decreased vision. Vision in the right eye was 20/40—2. Tension was 20.4 mm. Hg (Schiøtz). There were vitreous opacities and absent foveal reflex. By June 25, 1956, there was further decrease to 20/50, with relative central scotoma to 1/330 white. On July 3, 1956, vision O. D. was 20/50, the pupil was peaked at 10 o'clock, and tension measured 14.2 mm. Hg (Schiøtz). Vitreous was adherent to the wound in many areas, and vitreous opacities were present. A macular hole or cyst was seen with the Hruby lens. Because of the vitreous opacities, it was impossible to distinguish whether this was a hole or a cyst. Follow-up was for 21 months, when vision O. D. was 20/70, with persistence of the macular hole or cyst.

CASE 6.—A 53-year-old Negro man with B. P. 110/65 and emotional stability had on Oct. 3, 1947, an intracapsular cataract extraction on the right eye, with loss of vitreous. Postoperatively vitreous was seen in the wound at 1 o'clock, where a small hyphema appeared. On Oct. 14, 1947, there was a normal central field and the fundus was normal. Vision O. D. was 20/100. On Nov. 17, 1947, the right eye appeared white, aqueous ray was negative, tactile tension was normal, and the vitreous was in the wound. The patient complained on March 8, 1948, of spots in front of the right eye. Tactile tension was normal, and no fundus lesions were seen. On May 9, 1949, vitreous opacities were noted. Vision O. D. was 20/50. The patient was readmitted on May 23, 1949, for an intracapsular cataract extraction on the left eye; the postoperative course remained uneventful. The right eye vision was 20/70, with a central scotoma to 3/330 white and 6/330 red. Tactile tension was normal, and there was no aqueous ray. Synechiae were seen at 2 o'clock, and the pupil was drawn up. The fundus was normal. By Aug. 4, 1949, vision O. D. was 20/30. Follow-up was for four and one-half years, when vision O. D. was 20/30 and the fundus was normal.

CASE 7.—A 55-year-old white man had B. P. 130/70. Physical examination was normal, and he had emotional stability. On Oct. 7, 1955, the patient underwent an uneventful intracapsular cataract extraction on the left eye, with no loss of vitreous. The postoperative course was benign. On Oct. 17, 1955, he was discharged with 20/70 vision, an intact vitreous face, and a round pupil. By Nov. 3, 1955, tactile tension was normal, the pupil was round, aqueous ray was negative, and the vitreous face was intact. On Nov. 28, 1955, vision O. S. was 20/20+. On Dec. 15, 1955, the patient returned, complaining of a red eye. Vision O. S. was 20/20. The left eye was slightly injected; tactile tension was normal, and the cornea seemed clear. Aqueous ray was negative, but the vitreous face was ruptured. Vitreous resided in the anterior chamber. The fundus was normal. Four days later the patient returned complaining of strain and redness in the left eye. Vision O. S. was 20/20—2. The left eye showed minimal injection. The pupil was round; tactile tension was normal, and there was slight protective ptosis. Anterior chamber was of normal depth, and there was no aqueous ray. The vitreous face was broken and bulged through the pupil, but there were no strands of vitreous to the wound. On Dec. 23, 1955, vision O. S. was 20/30. By Dec. 28, 1955, the left eye was asymptomatic and vision was 20/20—3. On Jan. 18, 1956, vision O. S. was 20/15. Vitreous was still noted in the anterior chamber, but there were no vitreous strands to the wound. Tension was 12 mm. Hg (Schiøtz). On April 25, 1956, the patient returned asymptomatic. Vision O. S. was 20/20—2; tension was 14 mm. Hg (Schiøtz), and no aqueous ray was seen. On Dec. 14, 1956, the patient complained of metamorphopsia of three weeks' duration. Vision O. S. was 20/30+3. Tension in the left eye was 10 mm. Hg (Schiøtz) and in the right eye was 14.4 mm. Hg (Schiøtz). On slit-lamp examination of the left eye, it was observed that the vitreous face was broken in the left eye and a strand of vitreous extended to the wound at 11 o'clock. There was peripapillary edema which extended toward the macula. The macula was yellow with some white dots on its surface. There was a central scotoma to 3/1000 white. The patient returned on Dec. 18, 1956, with improvement of his vision to 20/15—1. Tension measured 13 mm. Hg (Schiøtz). The edema had disappeared. Two months later he experienced a decrease in vision, in the left eye. He had an inferior retinal detachment, and no definite holes were seen. A scleral resection was performed. The follow-up after cataract extraction was 18 months.

CASE 8.—A 64-year-old white woman with B. P. 140/80, mild arteriosclerosis, alcoholism and emotional lability had on July 8, 1953, an attempted intracapsular cataract extraction on the right eye. Postoperative course was uneventful, and vision O. D. was restored to 20/15. On Oct. 25, 1955, the patient had a combined intracapsular cataract extraction, with loss of vitreous, in the left eye. Tactile tension was soft on Nov. 10, 1955, and the eye was injected. On Dec. 1, 1955, the eye was "sore," vision O. S. was 20/40—2, the eye was injected, tactile tension was normal, and vitreous extended to the wound. Aqueous ray was negative, and the fundus was normal. On Feb. 7, 1956, the left eye was painful; tension in the left eye was 23 mm. Hg (Schiøtz), vision O. S. was 20/70, and there was a positive aqueous ray. The vitreous and fundus were as described before. The condition remained the same until June 6, 1956. The left eye was still "sore," and vision O. S. was 20/100. Tension O. S. was 14.2 mm. Hg (Schiøtz). There was edema around the disc and in the macula and persistent iridocyclitis. On June 9, 1956, tension in the left eye was 34 mm. Hg (Schiøtz), and on tonography C was 0.12. There was a central scotoma in the left eye to 3/1000 white, red, and blue. The patient was treated with systemic and topical administration of cortisone and local administration of atropine. On Feb. 7, 1957, vision O. S. was 20/200. There was an absent foveal reflex in the left eye, but no edema appeared in the disc or macula. Tension was 24 mm. Hg (Schiøtz). The left eye was injected, but aqueous ray was negative. Vitreous was adherent to the wound. Vision was 20/200 in the left eye. Follow-up was for 16 months, when vision O. S. was 20/200, there was an absent foveal reflex, and vitreous extended to the wound.

CASE 9.—A 67-year-old white man with B. P. 150/80 had slight arteriosclerosis and emotional stability. On April 10, 1953, an uneventful intracapsular cataract extraction was performed on the left eye, without loss of vitreous. On the first postoperative day there was transient shallow anterior chamber. On April 15, 1953, an uneventful intracapsular cataract extraction was performed on the right eye, without loss of vitreous. On April 24, 1953, vision O. D. was 20/50—1 and vision O. S. was 20/100—1. In the right eye the anterior vitreous face was intact and bulged slightly into the anterior chamber. In the left eye the vitreous face was broken and there was vitreous in the anterior chamber, mostly above. Tension O. D. was 16 mm. Hg (Schiøtz); tension O. S., 14 mm. Hg (Schiøtz). Both discs were well outlined and of normal size, shape, and color, with physiological cupping. The vessels were arteriosclerotic, but no gross lesions were seen. On May 4, 1953, vision O. D. was 20/100—1 and vision O. S. was 20/200. Discs were normal, and no gross lesions were noted in the maculae. The

right eye had a positive aqueous ray and an intact vitreous face. The left eye had a negative aqueous ray and vitreous filled four-fifths of the anterior chamber. On June 1, 1953, vision O. U. was 20/200. Tactile tension was normal. The vitreous face in the right eye bulged extremely, and the aqueous ray was negative. The left eye was as before. On June 22, 1953, vision O. U. was 20/70. The vitreous face was broken in the right eye, and vitreous opacities were noted. By July 20, 1953, vision O. D. was 20/200 and vision O. S. was 20/100. Vitreous was in the anterior chambers. The nerve heads appeared normal. Both eyes had a central scotoma to 3/330 white. Tactile tension was soft bilaterally. The patient was treated with cortisone locally and cyanocobalamin (vitamin B_{12}). On Aug. 17, 1953, vision O. D. was 15/200 and vision O. S. was 12/200. Tension in both eyes was 15 mm. Hg (Schiøtz). There was a definite cystic appearance in the macula of both eyes. On Sept. 17, 1953, vision O. U. was 20/200 and both vitreous faces were described as intact (late recondensation). Vitreous opacities were noted; the discs were blurred, and macular cysts existed in both eyes. An exudate was nasal to the disc in the left eye. Central scotomas were present in both eyes. By March 11, 1954, vision O. D. was 20/70 and vision O. S. was 20/100. One year later vision was unchanged and there were bilateral macular cysts. On July 13, 1956, vision O. U. was 20/70. Tension O. U. was 20.1 mm. Hg (Schiøtz). The discs were normal, but the maculae had absent foveal reflexes. Follow-up was for four years, when vision O. U. was 20/70. Macular degeneration and central scotomas were bilateral.

Case 10.—A 71-year-old white woman was emotionally labile and had slight arteriosclerosis. She had on Nov. 5, 1952, an uneventful intracapsular cataract extraction on the right eye. On Nov. 20, 1952, the vitreous bulged into the anterior chamber. On Dec. 2, 1952, she noted "black sparks" in the right eye, the fundus was normal, and vision O. D. was 20/30. The hyaloid face was formed, and vitreous bulged into the anterior chamber. Tactile tension was normal. On March 1, 1954, she noted decreased vision in the right eye. On March 5, 1954, vision O. D. was 20/60. There was edema of the disc and macula in the right eye. Treatment consisted of cortisone and cyanocobalamin. On March 9, 1954, a small hemorrhage appeared temporal to the disc, papilledema persisted, vision was 20/200, and there was a central scotoma. The left disc and macula were normal. On March 30, 1954, vision O. D. was 20/400. Skull x-rays were normal. Two abscessed teeth were removed. By May 11, 1954, vision O. D. was 20/400. Impression was either senile optic neuritis or vascular occlusion in the disc and possibly macular changes following cataract extraction. On Sept. 28, 1954, there was moderate optic atrophy in the right eye, and by June 9, 1955, vision O. D. was counting fingers at 1 ft. and vision O. S. was 20/60, owing to a senile cataract. Follow-up was for two and one-half years, when vision O. D. was counting fingers at 1 ft., with optic atrophy.

Case 11.—A 58-year-old white man had a normal physical examination and emotional stability. On Feb. 11, 1954, the patient underwent an uneventful intracapsular cataract extraction on the right eye. There was some postoperative redness in the right eye for two to four weeks, but on April 2, 1954, vision O. D. was 20/25. The patient was asymptomatic until May 11, 1954, when he returned complaining of blurred vision in the right eye of two days' duration. Vision in the right eye was 20/25; there was edema of the disc and a flame-shaped peripapillary hemorrhage. The patient was treated with cortisone, corticotropin (ACTH), and nicotinic acid. By May 31, 1954, the papilledema had subsided but the disc was pale. On June 18, 1954, vision O. D. was 20/60, with pale disc and granular macula. The hyaloid face was intact. There was a central scotoma to 1/330 white. Tension in the right eye was 20 mm. Hg (Schiøtz). The patient was thought to have had a vascular occlusion in his optic nerve. On July 18, 1954, the patient had an uneventful intracapsular cataract extraction on the left eye. On the seventh postoperative day a hyphema appeared. On July 26, 1954, the vitreous face was intact in the left eye. The hyphema was resorbing. By July 27, 1954, vision O. S. was 20/25. On Aug. 17, 1954, vision O. D. was 20/25 and vision O. S. was 20/20. On Oct. 29, 1954, vision O. D. was 20/80 and vision O. S. was 20/20. By the addition of a plus sphere vision O. D. was 20/40. On Dec. 17, 1954, the patient complained of poor vision in the right eye for five days. Vision O. D. was counting fingers at 8 ft. There was a central scotoma to 9/330 white. Treatment was with cyanocobalamin and hydrocortisone. By Dec. 21, 1954, vision O. D. was 20/50. By Dec. 30, 1954, vision O. D. was 20/40. On May 20, 1955, the patient complained of gradual onset of blurring in the left eye for the previous 10 days. Vision O. D. was 20/40; vision O. S., 20/25 with difficulty. The left disc was blurred, with a few linear hemorrhages near the border. On the temporal side of the macula there were pale curved exudates. By June 9, 1955, vision O. S. was 20/25 and the papilledema had cleared. Follow-up on the right eye was for 10 months, when vision O. D. was 20/40, with partial optic atrophy. Follow-up on the left eye was for 11 months, when vision O. S. was 20/25, with no papilledema or atrophy.

CASE 12.—A 60-year-old white man had emotional stability, moderate tortuosity of the retinal vessels, and an uneventful cataract extraction, right eye, in May, 1955. Vision O. D. was 20/25 until March, 1956, when it diminished to 20/200. There was an iris adhesion to the wound superiorly; the vitreous face was intact, and tension was 18 mm. Hg (Schiøtz). The right disc was blurred. There was a 5- to 10-degree central scotoma, but the macula was not remarkable. Treatment consisted of steroids and vitamins. In May, 1956, the patient had a cataract extraction on the left eye, with moderate postoperative reaction. In June, 1956, he had discomfort in the right eye. The vitreous face was broken, and vitreous almost filled the anterior chamber. Vision O. D. was 20/100. In December, 1956, vision O. D. was 20/60 and vision O. S. was 20/20. The right disc margins were still indistinct. Follow-up was for 19 months, when vision O. D. was 20/60; there were persistent papilledema and vitreous in the anterior chamber.

CASE 13.—A 78-year-old white man had mild arteriosclerosis, B. P. 160/100, and emotional lability. On Nov. 3, 1954, the patient had a combined intracapsular cataract extraction on the left eye. The lens was partially subluxated, but the operation was uneventful. On Nov. 5, 1954, the patient had an anterior chamber hemorrhage in the left eye. On Nov. 15, 1954, vision O. S. was light perception and good projection. The fundus could not be visualized because of blood in the vitreous. Vision in the left eye gradually improved to 20/30. It was noted that vitreous was in the anterior chamber. On June 18, 1955, the patient had a combined attempted intracapsular cataract extraction on the right eye. Vitreous presented, and the capsule broke, with cortical and capsular remains. On Aug. 26, 1955, vision O. D. was 20/20—2. On Sept. 15, 1955, vision O. D. was 20/100 and vision O. S. was 20/20. On Nov. 14, 1955, the patient was again seen and vision O. D. was 20/200 and the eye was slightly injected. There were vitreous floaters and strands of vitreous to the wound. The aqueous ray was negative. The patient returned on Jan. 16, 1956, complaining of further decrease in vision in the right eye. At this time vision O. D. was 16/200. The eye was moderately injected. There was a filtering bleb at the limbus at 12 o'clock; however, the anterior chamber was deep. There were capsular remains and vitreous strands to the wound. Tension was 11.9 mm. Hg (Schiøtz) in both eyes. Aqueous ray was 1+; the media appeared hazy, and there were degenerative changes near the macula. The vessels appeared sclerotic. On Jan. 23, 1956, there was a 3-degree central scotoma to 9/1000 white and 18/1000 blue. Vision O. D. was 10-12/200; there was a 2+ ciliary flush, with a deep anterior chamber, but the filtering bleb at 12 o'clock was still seen. By Jan. 24, 1956, the tension was 14.4 mm. Hg (Schiøtz) in both eyes. There was a questionable hole in the right macula. The disc appeared blurred. On Feb. 10, 1956, vision O. D. was 10-12/200. There was a persistent ciliary flush and positive aqueous ray, with a few cells in the anterior chamber. The macula appeared waxy, and a flame-shaped hemorrhage was seen above the disc. A lens protein skin test was negative. The patient had a negative survey for uveitis. On June 26, 1956, vision O. D. was 10/200 and tension was 11.9 mm. Hg (Schiøtz). With a Goldmann lens, macular edema and papilledema were seen. On Feb. 12, 1957, vision O. D. was 5/200, the eye was injected, aqueous ray was positive, and there was a negative fluorescein test. There was a small bleb over the 12 o'clock suture tract. Vitreous was degenerated and extended to the wound. Tension O. U. was 8 mm. Hg (Schiøtz). The right fundus was indistinct; the disc was hyperemic, and there was a macular cyst. Follow-up for the right eye was for two and one-half years, when vision O. D. was 5/200. There were hypotony, a bleb at the limbus, a hyperemic disc, and a macular cyst. Follow-up for the left eye was for three and one-half years, when vision O. S. was 20/20, with hypotony and vitreous in the anterior chamber.

CASE 14.—A 61-year-old white woman with B. P. 135/70, normal retinal vessels, and emotional stability, had on Aug. 13, 1956, an intracapsular cataract extraction on the right eye. The course was uneventful until Sept. 10, 1956, when vision O. D. was 20/200 with temporary glasses. The aqueous ray was negative; the vitreous face was intact; there was papilledema in the right eye, with a small peripapillary hemorrhage. By Oct. 23, 1956, vision O. D. was 20/15, the anterior chamber was well formed, and the disc was flat, with some indistinctness of the superior and nasal margins. Tension O. D. was 14 mm. Hg (Schiøtz); tension O. S., 20 mm. Hg (Schiøtz). Follow-up was for six months, when, on Feb. 12, 1957, vision O. D. was 20/15, the fundus was normal, tension was 14 mm. Hg (Schiøtz), and the vitreous face was intact.

CASE 15.—A 63-year-old white woman with B. P. 140/70 and slightly attenuated retinal vessels on Oct. 22, 1946, had an uneventful intracapsular cataract extraction on the left eye, without loss of vitreous. Disc, macula, and tactile tension were normal on Nov. 5, 1946, when vision O. S. was 20/30—3. On Nov. 18, 1946, the aqueous ray was not remarkable, tactile tension was normal, and there was papilledema. On Dec. 2, 1946, papilledema was still present. The hyaloid face was intact. On Aug. 30, 1949, vision O. S. was 20/30; the disc, retinal vessels, and macula were normal. The vitreous face was broken, and

anterior vitreous strands were noted. The anterior vitreous was cloudy; tactile tension was normal; visual fields were normal. Follow-up was for four years, when vision O. D. was 20/20 and the fundus was normal.

CASE 16.—A 50-year-old white woman with normal blood pressure and emotional lability had on March 1, 1956, an uneventful intracapsular cataract extraction on the left eye. On March 8, 1956, an uneventful intracapsular cataract extraction was performed on the right eye. On March 19, 1956, she noted cloudy vision in the right eye. On March 21, 1956, the right eye vision was distorted, vision O. D. was 20/400, vision O. S. was 20/30, and tension was 0 (Schiøtz) in the right eye and 18 mm. Hg (Schiøtz) in the left eye. The anterior chamber was of normal depth in each eye, and a fluorescein test was negative in the right eye. On March 23, 1956, tension in the right eye was 4 mm. Hg (Schiøtz), there was papilledema in the right eye, and all sutures were said to have been removed. By March 27, 1956, tension O. D. was 6 mm. Hg (Schiøtz). By April 10, 1956, tension O. D. was 17 mm. Hg (Schiøtz). Vision O. D. was 20/30+3, and papilledema had disappeared. By May 8, 1956, vision O. U. was 20/20; tension O. D. was 17 mm. Hg (Schiøtz). Follow-up was for one month, with normal vision, tension, and disc.

CASE 17.—A 53-year-old white man with normal physical examination, B. P. 130/80, and emotional stability had on May 1, 1946, an uneventful intracapsular cataract extraction on the left eye. The patient was admitted to the hospital again on April 24, 1947, for cataract extraction on the right eye. Vision O. D. was 2/200; vision O. S., 20/15. Both fundi were normal; fields were normal in both eyes, and tactile tension was normal O. U. On April 25, 1947, in the operating room it was noted that the pupil in the right eye was maximally dilated. After 0.25 cc. of procaine (Novocaine) was injected retrobulbarly, it was noted that the cornea was opaque and that tactile tension was stony hard and measured greater than 90 mm. Hg (Schiøtz). It was felt that there possibly could have been inadvertent injection of procaine intrabulbarly. The patient was immediately given 0.25% physostigmine (Eserine) locally, and in five minutes the tension had fallen in the right eye to 30 mm. Hg (Schiøtz) and the cornea became clear. It was suggested that preoperative dilatation of the pupil might have accounted for the rise in tension; however, preoperatively the anterior chamber was reported to have been of normal depth. The patient was given 10% furtrethonium (Furmethide), and the operation was canceled. After taking 10% furtrethonium every two hours the patient's tension was 18 mm. Hg (Schiøtz) within eight hours. On April 26, 1947, the tension measured 11 mm. Hg (Schiøtz). On the next day tension remained 11 mm. Hg (Schiøtz), and furtrethonium was decreased to three times a day. On April 28, 1947, the tension measured 10 mm. Hg (Schiøtz) and homatropine 5% was instilled in the right eye. Four hours later the tension measured 12 mm. Hg (Schiøtz). On April 29, 1947, the patient underwent an uneventful intracapsular cataract extraction with basal iridectomy in the right eye. The postoperative course was likewise uneventful. On May 10, 1947, at the time of suture removal the anterior chamber became flat, but it reformed the following day. On May 11, 1947, the patient was discharged and the fundus was normal. The anterior face of the vitreous was intact but bulged slightly into the anterior chamber. The patient returned on May 19, 1947, with the right eye injected and tension zero to fingers. The anterior chamber was shallow; the aqueous ray, negative; the hyaloid face was intact. There were 3 to 4 D. of papilledema, with folds in the retina and choroid. By May 26, 1947, the fundus was unchanged. On June 2, 1947, the right eye appeared white and tactile tension was low but palpable. The anterior chamber appeared deeper, and papilledema had decreased. It was noted that there was migration of pigment in the midperiphery. Temporally there was a pigmented area where, the observer stated, the globe might have been perforated. On June 16, 1947, vision O. D. was 20/20 and the anterior chamber was of normal depth. The papilledema had completely disappeared. There was some mottling of pigment in the midperiphery of the retina; however, no other changes were noted. Follow-up was for four months, when vision O. D. was 20/15 and there were no abnormalities noted.

CASE 18.—A 71-year-old white man's general physical examination revealed emphysema, B. P. 180/110, generalized arteriosclerosis, carcinoma of the prostate, and emotional stability. On July 7, 1948, the patient underwent an attempted intracapsular cataract extraction on the right eye; however, the anterior capsule tore and the posterior capsule remained intact. The operation otherwise was uneventful, and the postoperative course was benign. On Sept. 13, 1948, vision O. D. was 20/30. The patient was then not seen for seven years. He returned on June 20, 1955, with a normal aphakic left eye, complaining of decreased vision in the right eye of a month's duration. Vision O. D. was 20/70; tension, 12 mm. Hg (Schiøtz) O. U. It was noted that the patient's right disc was very pale. There was generalized arteriolar narrowing throughout the fundus. Visual fields revealed marked constriction to 18/330 white. The macular region appeared to be normal in the right

eye. Serum test for syphilis was negative; spinal fluid determinations were normal. On tonography C was 0.19. Skull x-rays were normal. The patient had a carcinoma of the prostate, without evidence of metastasis. Follow-up was for seven years, when vision O. D. was 20/70, with optic atrophy. The left eye was aphakic, with a normal fundus.

Comment

The Table shows that the cases in Group I, include those eyes with macular edema or cystic degeneration related to cataract extraction. We have listed under "cause" possible contributory factors.

Summary of Cases

Case	Onset	Best Vision After Operation	Final Vision	Fundus	Cause
Group I (Cases 1-6): Macular edema following cataract extraction					
1	0-2 mo.	20/50—1	20/70	Macular edema with cysts → cysts	Vitreous rupture; strands in anterior chamber
2 O. S.	6 mo.	20/20	20/15	Macular edema → normal (2 wks.)	Vitreous bulge → ? rupture
O. D.	3 mo.	20/20	20/15	Macular edema → normal (2 wks.)	? Vitreous rupture
3	2 mo.	20/20	20/200	"Central serous retinopathy" (19 mo.)	Vascular; late vitreous rupture; iridocyclitis
4	2 mo.	20/15	20/40	Macular cysts	Vitreous rupture; no strands in anterior chamber; iridocyclitis
5	15 mo.	20/30	20/70	No foveal reflex, hole or cyst (1 mo.)	Late vitreous rupture; strands to wound
6	5-19 mo.	20/50	20/30	Central scotoma	Vitreous loss; strands to wound
Group II (Cases 7-9): Macular edema and papilledema following cataract extraction; predominance of macular edema.					
7	14 mo.	20/15	20/20	Macular peripapillary edema → no edema → retinal detachment (2 mo.)	Late vitreous rupture; strands to wound; ? hypotony (T=10 mm. Hg); ? retinal detachment
8	9 mo.	20/40—2	20/200	Macular and peripapillary edema → no foveal reflex	Vitreous loss; strands to wound; iridocyclitis
9 O. D.	3 mo.	20/50—1	20/70	Macular cysts & peripapillary edema → macular degeneration	Vitreous bulge extreme; late vitreous rupture
O. S.	3 mo.	20/100—1	20/70	Macular cysts & peripapillary edema → macular degeneration	Vitreous rupture
Group II (Cases 10-12): Macular edema and papilledema following cataract extraction; predominance of papilledema					
10	17 mo.	20/30	Counting fingers at 1 ft.	Papilledema & macular edema → optic atrophy	Prior vitreous bulge → rupture; ? vascular insufficiency at disc; ? hypotony (T unknown)
11 O. D.	3 mo.	20/25	20/40	Papilledema, peripapillary hemorrhages, granular macula → pale disc (3 wk.)	? Vascular; ?? hypotony (T=20 mm. Hg [Schiøtz] 1 mo. later).
O. S.	10 mo.	20/20	20/25	Papilledema, peripapillary hemorrhages, exudate near macula → normal (3 wk).	? Vascular; ?? hypotony (T unknown)
12	9 mo.	20/25	20/60	Papilledema, 5- to 10-degree central scotoma → persistent papilledema for 10 mo.	? Vascular; late vitreous rupture sustained edema
Group II (Case 13): Macular edema and papilledema following cataract extraction					
13	3 mo.	20/20—2	5/200	Papilledema & macular edema → macular cyst, hyperemic disc	Hypotony (T=8-14 mm. Hg) with late fistulization; vitreous presentation; strands to wound
Group III (Cases 14-17): Papilledema following cataract extraction					
14	4 wk.	20/200	20/15	Papilledema → normal (1-6 mo.)	? Hypotony (T=14 mm. 6 wk. later; T=20 mm. in eye not operated on)
15	3 wk.	20/30	20/20	Papilledema → normal	? Hypotony (tactile tension normal)
16	1½ wk.	20/400	20/20	Papilledema → normal (3 wk.)	Hypotony (T=0) (anterior chamber normal depth; fluorescein test negative)
17	3 wk.	20/100+1	20/15	Papilledema → normal (1 mo.)	Hypotony (T=0); ? intraocular procaine; ? angle-closure glaucoma preoperatively
Group IV (Cases 10, 11, 18)*: Optic atrophy following cataract extraction					
18	7 yr.	20/30	20/70	Optic atrophy	? Vascular insufficiency in disc

* See Cases 10 and 11 in Group II.

The vitreous face was broken at the onset of macular disturbance in four eyes. Two of these eyes (Cases 5 and 6) showed vitreous adhesions to the wound. In the other two eyes no adhesions were seen. In Case 3 the vitreous face was intact at the onset of macular edema but developed late rupture, which may have played some part in the prolonged course for 19 months. In the two eyes in Case 2 the state of the vitreous was not mentioned at the time of the onset of edema. Prior to this, however, there had been an extreme herniation of the face. It is possible that these eyes may have had ruptured vitreous faces at the time of onset of macular edema. Tension was normal in five of the seven eyes, while in two eyes it was not recorded. There was some associated iridocyclitis in two cases. Onset of edema was within 3 months of surgery in four eyes, within 6 months in two additional eyes, and at 15 months in one eye. Visual results were good except in the cases where macular cysts developed.

Group II contains nine eyes in seven cases with macular edema and papilledema following cataract extraction. The Table shows four eyes in which macular edema was predominant. Tension was normal in three of these eyes and 10 mm. Hg (Schiøtz) in the fourth eye. All four eyes had ruptured vitreous faces at the onset of edema, with the exception of one eye, in which an extreme herniation ruptured shortly after edema appeared. Two of four eyes had vitreous strands to the wound. One eye had a persistent iridocyclitis from the time of surgery, but edema did not develop until nine months postoperatively. In Case 7 a retinal detachment was detected two months after the macular edema was noted. The detachment and macular edema may have been related to the same cause, namely, vitreous traction. We feel that the contributory causes in these eyes were the abnormal state of the vitreous and, in one case, prolonged iridocyclitis.

The Table lists four additional eyes in which papilledema was predominant. In two eyes the papilledema progressed to optic atrophy. It was impossible to evaluate the influence of the state of the vitreous or the intraocular pressure on the onset of edema because of insufficient data. Iridocyclitis was not a feature in these cases. Vascular insufficiency in the disc was probably responsible for edema and subsequent optic atrophy.

In the remaining eye in Group II papilledema and macular edema were equally prominent. There was vitreous to the wound and late fistulization with hypotony, all of which we regarded as contributory to edema.

Group III (Table) contains four eyes with papilledema, in four cases. There was a tension of zero at the onset in two eyes. When tension returned to normal, papilledema disappeared and vision was restored. Tension was not recorded in the other two eyes. Case 17 was most unusual in view of the preoperative complications (see case reports).

Group IV (Table) includes three eyes with optic atrophy (Cases 10, 11, and 18). Cases 10 and 11 were discussed in Group II. The remaining eye was found to have optic atrophy when the patient was seen seven years after operation. Although he had clinically a carcinoma of the prostate, there was no evidence of metastasis. Survey for other causes of optic atrophy was negative except for generalized arteriosclerosis. It is possible that this patient's optic atrophy was of vascular origin. Since no tension was recorded postoperatively, we can only speculate as to the relationship of hypotony.

The age of our patients ranged from 50 to 78 years. Twelve were men, and six were women. All had senile cataracts. Eighteen eyes had intracapsular cataract extractions, and three had attempted intracapsular cataract extractions. There seemed to be no correlation of elevated blood pressure or emotional status with macular edema. Vitreous was lost in three eyes at surgery.

The clinical appearance of macular edema following cataract extraction is identical to the lesion of so-called central serous chorio-

retinopathy in phakic eyes. Histological examination of the latter group reveals that there is no true edema of the macula but rather a serous detachment from Bruch's membrane or the pigment epithelium.[14] The etiology of central serous chorioretinopathy is believed by the majority of investigators to be a choroidal vascular disturbance.[15,16] Serous detachment of the macula would therefore seem to be a more appropriate term than macular edema following cataract extraction, although the latter is in common usage in the literature and is incorporated in this paper.

The state of the vitreous may be of prime importance in the development of macular edema. Thus, macular edema and associated peripapillary edema may be precipitated by a ruptured vitreous face, particularly when there are vitreous adhesions to the wound. Irvine emphasized this, and several of our cases lend support to this concept. Such vitreous abnormalities may produce changes at the posterior pole by creating traction at the macula and disc, for Grignolo[17] has demonstrated vitreous attachment at the macula as well as about the disc and ora serrata. A second possibility is that the abnormal state of the vitreous may produce a vasomotor instability in the choroid which results in a serous detachment of the macula. Just what the exact relationship is between the abnormal vitreous and the production of vasomotor instability cannot be stated. Perhaps hypotony is associated. However, in our cases of macular edema persistent hypotony was not present. A transient hypotony at the time of vitreous membrane rupture may have occurred. Macular edema may follow cataract extraction without rupture of the vitreous face, as occurred in one of our patients. In this case the later rupture may have perpetuated the edema. The evidence presented strongly suggests that a disturbance in the vitreous is at least in part a causative factor. The importance of posterior detachment of the vitreous with or without rupture of the vitreous face cannot be evaluated, because of the infrequency of Hruby lens examination in the cases presented.

Iridocyclitis was a noteworthy feature in three cases. It is possible that an irritative condition of this type may have caused a vasomotor instability in the choroid, resulting in a serous detachment of the macula.

We have included cases of papilledema following cataract extraction in some of which hypotony was definitely related. One case had late fistulization with bleb formation and represents the syndrome presented by Dunnington. The other cases may have had intermittent wound leakage, but we lacked evidence to support this. If hypotony alone were the cause of aphakic papilledema, one might expect to encounter papilledema frequently in the postoperative state. Perhaps the qualifying factors are the degree of reduction of tension, duration of hypotony, relationship to preoperative tension, and vascular response at the disc. In two of our cases papilledema progressed to optic atrophy. The atrophy probably resulted from vascular insufficiency at the disc in arteriosclerotic patients.

Prognosis for vision is favorable in those patients in whom the macular detachment is transient. However, macular cysts and degeneration may result if the serous detachment persists for several months. In those patients with visual loss due to papilledema from hypotony the visual acuity may be restored when tension returns to normal and papilledema disappears. The appearance of optic atrophy obviously carries a poor prognosis for vision. There are certain aspects of these problems which remain unsolved. Ordinary direct ophthalmoscopy is often inadequate for detecting serous detachment of the macula following cataract extraction. Hruby lens examination and indirect ophthalmoscopy are preferred. It is hoped that careful analysis of future cases may provide us with additional knowledge.

Summary

A review of the literature on macular edema, papilledema, and optic atrophy following cataract extraction is presented.

Eighteen cases, 21 eyes, are presented and analyzed. These were obtained from a review of 1600 ward cases and additional cases from the private service.

Serous detachment of the macula is a more appropriate term than macular edema following cataract extraction, although the latter term is in common usage.

The state of the vitreous, choroidal vascular instability, and iridocyclitis are considered as they relate to serous detachments of the macula (macular edema).

Persistent hypotony does not seem to be a feature in the cases with macular edema alone.

Hypotony is a cause of papilledema following cataract extraction.

Optic atrophy may occur after cataract extraction and may be associated with papilledema and vascular insufficiency at the disc.

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The Distribution of Lipids in the Bovine Lens and Cornea

A Histochemical Study

A. J. DARK, F.R.C.S. (Ed.), D.O. (London), Oxford, England

As a result of biochemical analyses of lipids in the bovine lens and cornea, Krause [1] and, more recently, D'Asaro et al.[2] have been able to show that phospholipids form a major constituent of the lipid fractions from the bovine lens and cornea. In the light of such biochemical information it is naturally of interest to determine the histochemical picture of lipid and phospholipid distribution in these two avascular structures. Apart from Wislocki's histochemical study on the anterior segment of the eye of the rhesus monkey,[3] in which reference is made to the distribution of Sudan black-positive material in the cornea and lens, no other attempt to localize lipid in these tissues on a cytological level seems to have been made. Furthermore, it has been recently established that an affinity for Sudan black may, on occasion, also characterize certain nonlipid substances [4]; additional tests are therefore required before accepting the specificity of Sudan black as a lipid stain.

The present study, involving the use of histochemical procedures, deals with the distribution of lipid in general and of phospholipid in particular in the bovine lens and cornea.

Methods and Materials

Twenty eyes were obtained from freshly slaughtered cattle. Thin segments of cornea were immediately prepared and immersed in fixing fluids. Lenses were placed entire in ice-cooled fixatives. On arrival at the laboratory they were frozen and then cut into thin slices (2 to 3 mm.) for adequate fixation in the various fixing fluids.

For the general distribution of lipids, tissue slices were fixed in calcium chloride-formol; some of this material was subsequently postchromed in accordance with the procedure requisite for Baker's acid hematein method.[5,6] Frozen sections [10] were stained with Sudan black B (British Drug Houses) as a saturated solution in 70% alcohol or, alternatively, in propylene glycol [7] for periods ranging from two minutes to half an hour. Staining was carried out at room temperature and at 60 C.

In some instances, after staining with Sudan black a sudanophilia of the relatively stable variety [4] was manifested; the dye could not be readily extracted from the sections by washing in 70% alcohol; under these circumstances the histochemical significance of this type of Sudan black staining requires further elucidation. When stable sudanophilia was encountered, its significance was evaluated by staining control sections with acetylated Sudan black,[8,9] a more specific reagent for lipids than the cruder, nonacetylated form, which is available commercially. The exclusive use of acetylated Sudan black as a substitute for the commercial form could not be undertaken, however, because the acetylated dye is apparently less sensitive than the commercial product. Control tissue fixed in Baker's weak Bouin fluid was extracted with hot pyridine (60 C) for 24 hours prior to staining frozen sections with Sudan black B.

The handling of free lens sections in Sudan black is difficult because of their

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Department of Histology, University College, Cardiff, Wales. Present address: Nuffield Laboratory of Ophthalmology, Oxford.

friability. When possible, sections were therefore affixed to albuminized slides and allowed to dry almost completely. If, at the appropriate moment, they are immersed in the staining jar, sections will remain adherent; but too much desiccation will result in curling and loosening of the sections. Free-floating sections were also used as controls to guard against artifacts resulting from the above procedures; the results were essentially similar apart from shrinkage fissures which tend to appear in the semidried material. Chromated material cannot be handled successfully by this method.

Phospholipids were localized with Baker's acid hematein method[5,6] controlled by his pyridine extraction procedure.

In addition to the main methods just described, certain other procedures, such as hematoxylin and eosin, the periodic acid-Schiff technique, and Wilder's reticulum stain, were carried out concurrently on both frozen and paraffin-embedded material. Observations following these ancillary methods will be mentioned only when it is considered that they provide information directly relevant to the main object of this study.

Observations

A. Cornea

Observations on the cornea were made on "vertical" and tangential sections. In the following account, three zones are recognized in the corneal epithelium: (1) a superficial stratum consisting of nucleated squames, 3 to 4 cells deep; (2) an intermediate stratum composed of polygonal cells, 14 to 19 cells deep; (3) the basal stratum, which is a single layer of columnar cells resting on Bowman's membrane. Tall pillar-like cells are interposed at frequent intervals among the cells of the basal layer; they extend into the stratum intermedium before splaying out to form ramifying strands with dense oval nuclei. The complicated architecture of these cells is best appreciated in tangential sections. These cells are characteristic for the bovine cornea and have been fully described by Frieboes.[10]

I. General Distribution of Lipid Following the Use of Sudan Black.—(*a*) Anterior Epithelium of Cornea: Cell interfaces (especially in the anterior layers of the stratum intermedium) are stained a grayish-blue, but in a pale shade, which made photography unsatisfactory. Only occasionally can intercellular bridges be resolved with certainty. Fine elongated black filaments can often be seen in the pillar-like cells, referred to above, and so in tangential sections the extensive branching of these cells among those of the deeper zones in the stratum intermedium forms a striking feature. Clusters of minute black spheres are sometimes aggregate at the poles of nuclei in the deeper zones of the stratum intermedium. The cytoplasm of all these cells, and more particularly the most superficial squames, is colored a pale slate-blue.

(*b*) Substantia Propria Corneae: Anterior to Bowman's membrane a fine dark gray line is often discernible in vertical sections; it corresponds to the fenestrated "membrane" described by LaTessa, Teng, and Katzin,[11] who, recognizing its lipid nature, also claimed to have demonstrated the presence of reticular fibers in it—a finding which neither in frozen nor in paraffin sections could be confirmed in the present study.

The most arresting feature made visible in the substantia propria corneae is the presence of numerous small lipid particles in the perikaryon and processes of the corneal "corpuscles" (Fig. 1); the cytoplasm of these cells is a pale gray-blue or unstained. In tangential sections the details of the intricate "syncytium" which these cells form is thereby made clearly discernible (Fig. 2).

(*c*) Descemet's Membrane and Endothelium: In contrast to the membrane, which is lipid-free, the endothelium is shown to be rich in fat, which is present in the form of many minute droplets disposed fairly evenly throughout the cytoplasm, though sometimes aggregated along the nuclear membrane. The fat droplets are usually spherical, but short chains of rod-like particles also occur, especially alongside the nuclear membrane (Figs. 3 and 4).

Fig. 1.—Tangential section of corneal stroma. A single corneal corpuscle; cytoplasm packed with numerous black particles. Sudan black B; × 1650.

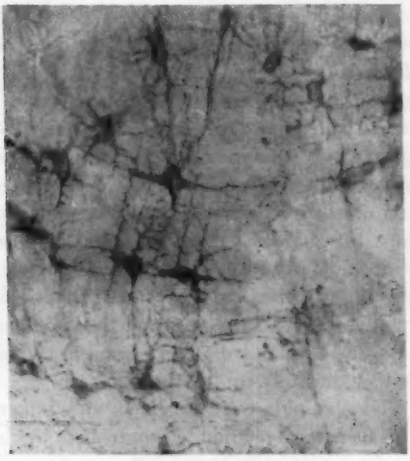


Fig. 2.—Tangential section of corneal stroma. The corneal corpuscles are shown up by virtue of numerous fine black particles in their cytoplasm. Sudan black B; × 210.

After pyridine extraction none of these structures of the cornea stained with Sudan black. Stable sudanophilia was not encountered in the cornea.

II. Phospholipids Demonstrated with Baker's Acid Hematein Method.—(*a*) Anterior Epithelium of Cornea: Cell interfaces are colored a blue-black, and this is especially intense in a rather restricted region comprising the anterior layers of the stratum inter-

Fig. 3.—Tangential section of Descemet's endothelium. The cytoplasm surrounding the characteristically shaped and eccentrically situated nuclear areas is filled with small lipid droplets, sometimes more densely aggregated in the perinuclear zone and at the cell interfaces. Sudan black B; × 950.

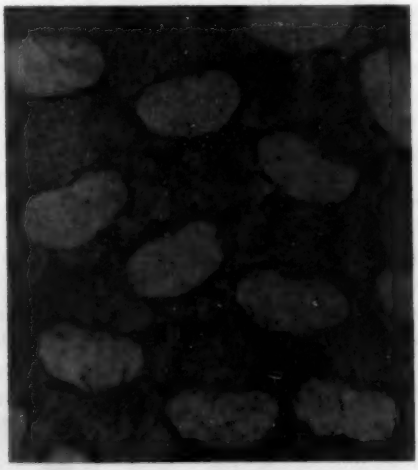
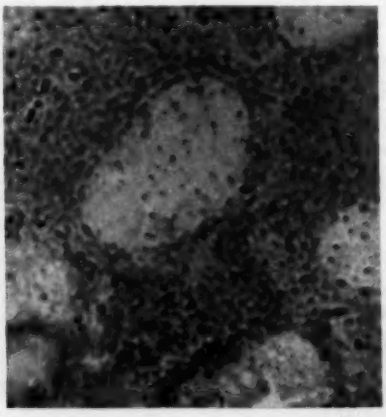


Fig. 4.—Tangential section of Descemet's endothelium. A chain of rod-like particles alongside the nuclear membrane is discernible. The cytoplasm is packed with numerous particles. Sudan black B; × 1800.



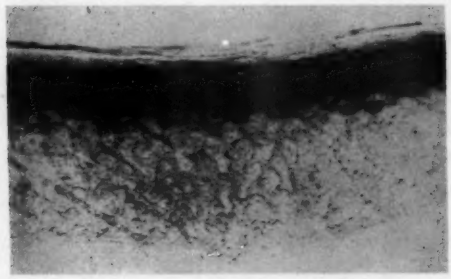


Fig. 5.—Vertical section of anterior corneal epithelium. Dense staining of intercellular bridges and tonofibrils in the anterior zone of stratum intermedium. Baker's acid hematein method; × 365.

medium (Fig. 5). Under high magnification this material is seen to be composed of intercellular bridges. Tangential sections through this layer provide a display of these intercellular bridges, which sometimes seem to show continuity with tonofibrils (Fig. 6). A few droplets are seen in the cytoplasm of cells in the basal stratum. The pillar-like cells of Frieboes are often intensely stained and stand out in a striking manner, but as they are usually similarly colored in the controls no conclusions regarding their phospholipid content can be drawn.

(*b*) Stroma: Corneal corpuscles can usually be clearly visualized by this method, by virtue of blue-black droplets in their cytoplasm, but it must be mentioned that they were not consistently demonstrated in all sections; so presumably their phospholipid content must be near the threshold sensitivity of this method.

Strongly positive corpuscles are most frequently observed in the vicinity of the basement membranes (especially Bowman's) and also near the cut edges of the tissue. (It was not possible to decide whether this was due to more rapid fixation at these sites or to some other unknown technical factor.)

(*c*) Descemet's Membrane and Endothelium: Phospholipid was not present in this membrane. The cytoplasm of the endothelial cells contains blue-black particles similar to those seen after Sudan black staining but less clearly differentiated from the general bluish background (Fig. 7).

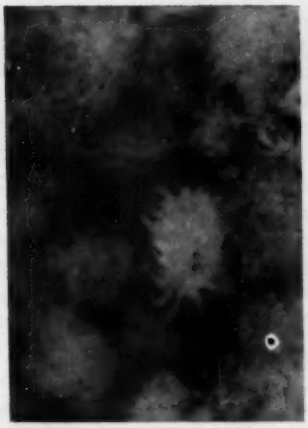


Fig. 6.—Tangential section of anterior corneal epithelium. Tonofibrils and intercellular bridges. Baker's acid hematein method; × 1700.

B. Lens

Observations have been made on the lens concerning the anterior epithelium and the cement substance between the lens fibers. Sections were cut in equatorial, meridional, and tangential planes.

1. General Lipid Distribution with Sudan Black.—(*a*) The Anterior Epithelium: The cytoplasm, which is itself colored a pale gray-blue, contains many discrete black granules (Fig. 8).

(*b*) Lens Cement Substance: Although the lens fibers themselves are not significantly stained, the cement material between adjacent prisms is stained gray-black. The cortical cement is more deeply stained than that in the lens nucleus. A conspicuous feature in lens sections is the presence of certain lipid corpuscles which are, seemingly,

Fig. 7.—Vertical section of deeper layers of cornea. Positive reaction in the endothelium of Descemet (arrow). Baker's acid hematein method; × 350.

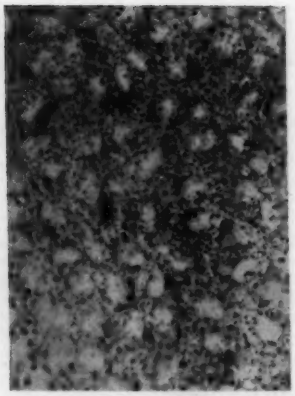
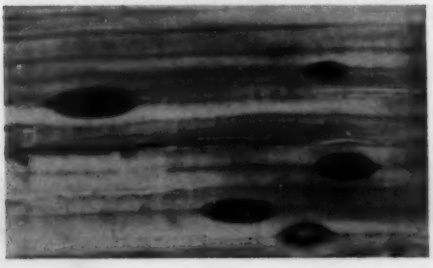


Fig. 8.—Tangential section of anterior lens epithelium. The presence of numerous black particles lying on a gray cytoplasmic background is shown. Sudan black B; × 570.

embedded in the cement substance. They are found in a restricted zone about 1 mm. wide which lies 2 to 3 mm. from the lens equator in a radial direction and extends a short distance backward and forward on either side of the equatorial plane. The corpuscles, which are oval in cross sections, lie alongside the broad sides of the unequal hexagons characteristic for equatorial sections through this region (Fig. 9). The bodies are preferentially elongated (2μ to12μ, average 10μ) in the meridional direction, and, as can be seen from the illustration (Fig. 10), they possess a denser outer zone and a paler central area. Although colored faintly with other Sudan dyes, they have a negligible affinity for hematoxylin and other basic dyes. The periodic acid-Schiff technique colors them faintly.

Fig. 10.—Meridional section of lens cortex. Cement substance and "corpuscles" are positive. Sudan black B; × 1520.



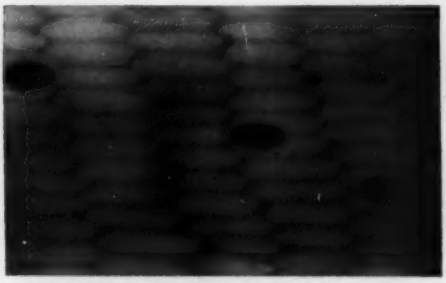


Fig. 9.—Equatorial section of lens cortex. Cement substance and "corpuscles" described in text are positive. Sudan black B; × 1500.

All these Sudan black-positive structures in the lens were relatively resistant to decolorization with 70% alcohol, but they could be readily demonstrated with the acetylated dye. After pyridine extraction no staining was present in any of these structures.

II. Phospholipids Demonstrated with Baker's Acid Hematein Method.—The cytoplasm of the anterior lens epithelium, which is stained a grayish color, contains closely packed blackish granules (Fig. 11).

The lens nucleus and the oval corpuscles just described are both stained an intense blue-black. However, both these structures are similarly stained in control material, and so no opinion regarding their phospholipid nature can be given. The cement substance between the lens fibers of the cortical region was unstained.

Fig. 11.—Tangential section of anterior lens epithelium. Numerous blue-black particles lie in the cytoplasm. Baker's acid hematein method; × 1750.

Comment

An interesting result of this histochemical study has been the discovery of Sudan black-positive (lipid) corpuscles which are intimately associated with the lens cement substance. These structures have been the subject of a previous communication,[12] in which it was mentioned that they had also been observed in the lenses of the cat and the dog. Further, it was noted that the corpuscles exhibited a surprising lack of affinity for the usual histological stains (including other dyes of the Sudan series), a fact which may explain why these curious structures have apparently been overlooked in the past. In appropriate Sudan black preparations they are conspicuous even under low magnifications. It is considered most unlikely that these structures are of a parasitic nature.* Remarks on the significance of these corpuscles are necessarily speculative. It is possible that they represent aggregations of lens cement material (which has similar, but less intense, staining properties), and one wonders whether they might have some connection with Sinclair's hypothetical "lens fluid," to which he attributes such an important role in accommodation.[13] The "cystoid spaces" recently described in human lenses by Reese and Wadsworth [14] are apparently much larger and have a different distribution; indeed, apart from a positive reaction following the use of the periodic acid-Schiff procedure, they do not appear to resemble the lipid corpuscles which are found in the ox lens.

The distribution of Sudan black-positive material in the lens and cornea of the rhesus monkey (Macaca mulatta) has been reported by Wislocki.[3] In the present study certain ancillary tests were performed in order to increase the specificity of Sudan black. To some extent the observations made on ox and rhesus material are similar: Fine lipid particles in the cytoplasm of the corneal corpuscles, the corneal endothelium, and the anterior epithelium of the lens are present in both animals. In the present study tangential sections have revealed the extensive nature of this distribution—particularly in the case of the corneal corpuscle "syncytium." In both animals the lens cement was stained with Sudan black. In other respects the distribution of lipid differs; the anterior epithelium of the cornea of the ox was characterized by the presence of lipid at cell interfaces, in the cells of Frieboes, and in the juxtanuclear (?Golgi) zones of cells in the deeper layers. In the rhesus monkey the whole epithelium was simply colored a "pale slate blue." The curious lens-shaped corpuscles which are embedded in the lens cement of the ox were not noted by Wislocki in the lens of the rhesus monkey.

The lipid nature of the fine "membrane" lying anterior to Bowman's membrane has been described by LaTessa, Teng, and Katsin,[11] and this was confirmed in the present study. However, the findings, by the same authors, of reticular fibers in this membrane could not be substantiated.

The specificity of Baker's method for demonstrating phospholipids has been confirmed by Cain [15] and by Cassellman [16] (the latter author noted that phosphatidic acids could also be demonstrated). In spite of these confirmatory studies, which were carried out on purified substances in model experiments, there is some evidence that in certain tissues phosphatides are present in a form which renders them inaccessible for demonstration with this technique.[17] We may, therefore, regard a definite positive result with this method as indicative of phospholipid, although a negative finding cannot be taken to exclude the presence of phospholipid absolutely.

The acid hematein method has indicated that most if not all of the lipid particles in the corneal corpuscles, Descemet's endothelium, and the anterior lens epithelium contain phospholipid. Some of these droplets may well be mitochondria, but pending further investigation they are best noncommittally termed lipochondria. The phospholipid nature of intercellular bridges has

* Prof. P. C. C. Garnham excluded a possible protozoal origin for these structures, and Dr. J. Walker was unable to identify them with any known species of fungus.

been demonstrated in epithelia other than that of the cornea.[18,19] It is therefore of interest to note that these structures and also the tonofibrils are shown to contain phospholipid in the bovine cornea.

It is not possible to correlate the histochemical findings with the functional aspects of these tissues, except that it may be mentioned in a general way that the high phospholipid content of the anterior corneal epithelium and Descemet's endothelium is in agreement with the highly active metabolic roles of these two surface layers already indicated by many well-known physiological phenomena in connection with water and ion exchange in the cornea. In view of the phospholipid nature of the intercellular bridges and tonofibrils it is perhaps possible that oil-soluble metabolites may use these fibrils as a preferential pathway and that oil-soluble drugs may similarly utilize this potential pathway to reach the anterior face of the corneal stroma.

Summary

Histochemical methods were used to elucidate the distribution of lipid in general and of phospholipid in particular in the bovine lens and cornea.

The occurrence of apparently hitherto unknown lipid corpuscles in a restricted zone of the lens is described.

A lipid component is present in the lens cement substance.

Tonofibrils and intercellular bridges in the corneal epithelium are shown to contain phospholipids.

A rich accumulation of phospholipid in the corneal epithelium, endothelium, and stromal cells and also in the anterior lens epithelium is noted.

Dr. F. Jacoby, of the Histology Department, University College, Cardiff, Wales, gave suggestions and help in the preparation of the manuscript, and Mr. L. Jones, of the same department, was responsible for the photomicrographs.

Nuffield Laboratory of Ophthalmology, Oxford.

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Further Perfusion Studies on the Outflow of Aqueous Humor in Human Eyes

J. FRANÇOIS, M.D.; M. RABAEY, M.D.; A. NEETENS, M.D., and L. EVENS, M.D., Ghent, Belgium

In previous publications it has been pointed out, on the basis of in vitro perfusion studies of enucleated eyes,[3,4] that the depth of the anterior chamber exerts a very considerable influence on the facility of aqueous outflow. We believe that this fact is sufficiently important to warrant a more detailed discussion; at the same time we shall give the results of a systematic investigation into the influence of the pressure of the perfusion fluid on the facility of aqueous outflow.

I. The Influence of the Depth of the Anterior Chamber

From the very beginning of our experiments we have been struck by the fact that the aqueous flow is as a rule considerably more important in eyes with deep anterior chambers than in eyes with anterior chambers of less depth.

This fact led us to begin experiments involving systematic modification of the depth of the anterior chamber by reducing the volume of the posterior half of the eyeball. At the level of the equator a guillotine forceps with a variable opening is placed; this makes it possible to increase or decrease the depth of the anterior chamber by increasing or decreasing the volume of the eyeball in that the iridocrystalline membrane is pressed forward to a more or less marked extent. Diminution of the depth of the anterior chamber immediately causes a slight increase in intraocular tension. It is therefore necessary to wait until the initial intraocular tension has been restored before the experiment is continued.

The depth of the anterior chamber is optically determined with the aid of a slit lamp and a binocular microscope fitted with a micrometric gradation. The distance between the anterior surface of the cornea and the anterior surface of the iris is measured, and the figure obtained is corrected to account for the error resulting from the curvature of the cornea.

The facility of outflow was determined in a series of different depths, and it was soon obvious that no other factor had such an evident effect on the rate of aqueous flow as the depth of the anterior chamber. It was always found that the resistance showed a marked increase to the extent to which the anterior chamber diminished in width. Even if the depth of the anterior chamber is normal or large, a slight contraction gives rise to a marked slowing of the outflow. These facts were regularly verified in more than 75 experiments.

The phenomenon is completely reversible in both directions. Restoration of the depth of the anterior chamber to a certain value is always associated with the same measured resistance. A characteristic example is given in Table 1 (Fig. 1).

TABLE 1.—*Relation of Facility of Outflow to Depth of Anterior Chamber*

Depth of Anterior Chamber, Mm.	Time Required for Outflow of 10 Cu. Mm. Fluid	C*	R*
4.25	1'8"	0.4	2.5
4.05	1'10"	0.38	2.63
3.2	1'30"	0.30	3.03
2.8	1'55"	0.23	4.3
2.3	2'17"	0.19	5.2
1.95	3'30"	0.13	7.6
1.7	3'50"	0.11	9.0

* C, outflow of aqueous humor, cubic millimeters per millimeter Hg per minute; R, resistance to outflow (R=1/C).

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From the Ophthalmological Clinic of the University of Ghent; Director, Prof. J. François. Investigator under the National Fund for Scientific Research (Dr. Rabaey).

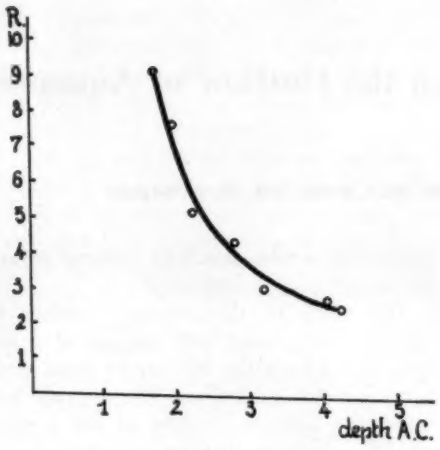

Figure 1

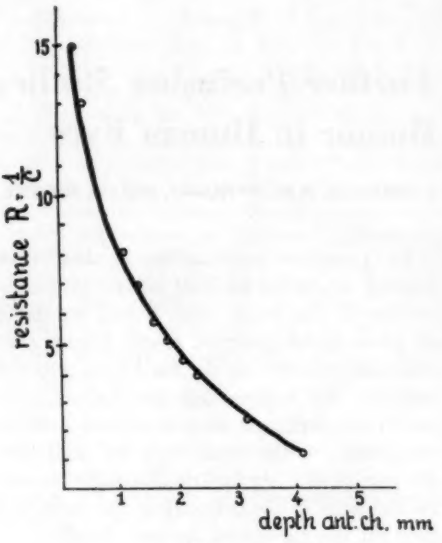

Figure 2

The first conclusion to be formed is that the values obtained for outflow (C) and resistance to outflow (R) during perfusion are themselves of little significance. In order to obtain comparable results it is absolutely necessary to consider the values as correlated with the depth of the anterior chamber.

This correlation was experimentally determined in 30 normal human eyes; the curve obtained is reproduced in Figure 2. It can be stated that the resistance to outflow averages 1 to 2 with a depth of anterior chamber of 4 mm. and more, 2 to 3 with a depth of 3 to 4 mm., 3 to 5 for a depth of 2 to 3 mm., 5 to 10 for a depth of 1 to 2 mm., and over 10 for a depth under 1 mm.

The second conclusion to be formed is that it is no longer possible to accept the classical conception according to which the angle must be completely closed over at least three-quarters of its circumference in order to cause considerable slowing down in the outflow, which should be more or less normal as soon as the slightest breach occurs in it.

The third conclusion to be reached is that in vivo tonography, if it is to be valuable, must take into account the depth of the anterior chamber. In view of our experiments it is clear that tonography yields pathological values for C and R when the anterior chamber is shallow. In this case, however, it is not so much the resistance to the aqueous flow which is pathological as the depth of the anterior chamber.

We had occasion to verify this point in a case of corneal herpes zoster complicated by hypertensive iridocyclitis. The hyperten-

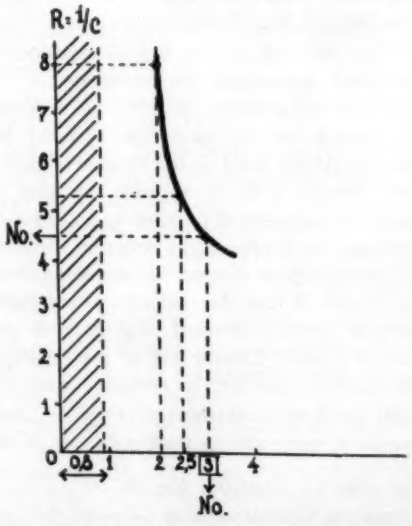

Fig. 3.—The abscissa shows the depth of the anterior chamber in millimeters. The shaded area shows the thickness of the cornea, which is not included in the measurement of the chamber.

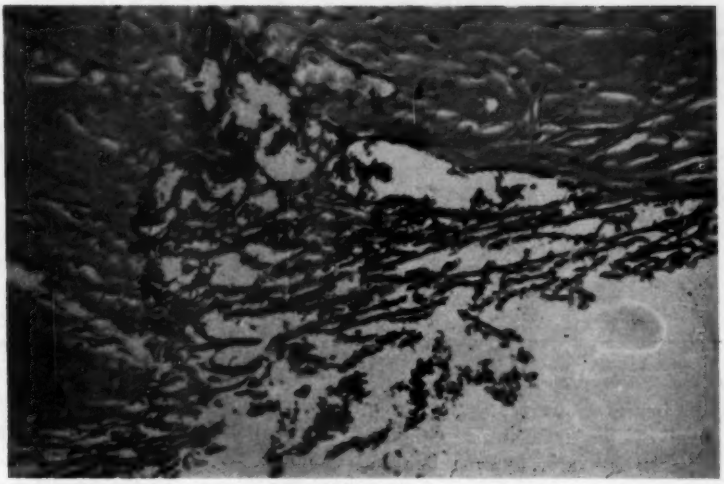

Figure 4

sion preceded the clinical symptoms of iridocyclitis and was due partly to hypersecretion of aqueous humor and partly to increased resistance. The anterior chamber was initially rather narrow and subsequently became deeper. Thus, the resistance to aqueous outflow was shown to be obviously proportional to the depth of the anterior chamber (Fig. 3): It was 8 with a depth of 2 mm., 5.3 with a depth of 2.5 mm., and 4.5 with a depth of 3 mm.

The importance of the depth of the anterior chamber is not surprising, as it constancy is the basis of the regulation of intraocular tension. Any change in the depth of the chamber is immediately compensated by a change in the resistance to outflow. If the anterior chamber becomes too deep, a decrease in resistance ensures a greater outflow of aqueous humor. On the other hand, should the chamber become too narrow an increase in resistance ensures a decrease in outflow.

Our experiments have shown that, on the other hand, this mechanism is completely

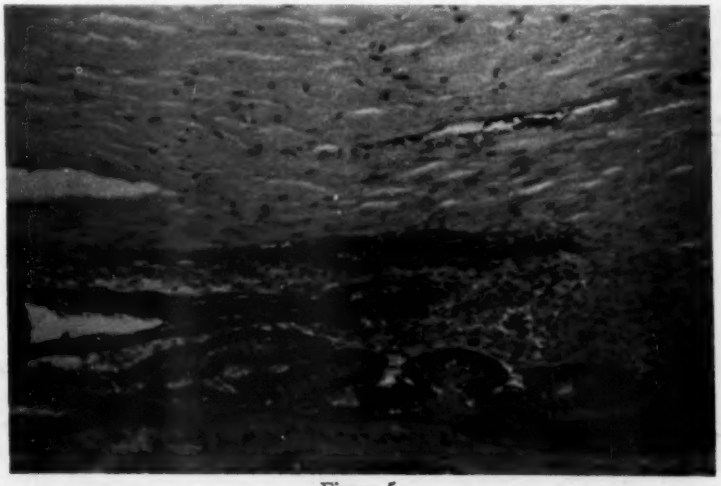

Figure 5

TABLE 2.—*Resistance to Outflow in Myopic Eyes*

Myopic Eye	Depth of Anterior Chamber, Mm.	*C*	*R*
1	4.7	0.60	1.66
	3.6	0.45	2.20
	2.7	0.28	3.57
	2.25	0.23	4.34
	1.95	0.15	6.66
	1.4	0.09	11.11
2	5.1	0.77	1.30
	3.4	0.35	2.85
	2.4	0.21	4.76
	1.65	0.15	6.66
	1.1	0.097	10.3
3	4.25	0.54	1.85
	3.15	0.34	2.94
	2.7	0.26	3.84
	1.55	0.14	7.14

independent of differences in tension and of vascular or neural influences.

At the level of the iridocorneal angle, therefore, there is an autoregulatory mechanism which maintains a constant depth of the anterior chamber. It is not yet known with any certainty what the anatomical substratum of this mechanism is. The unfolding of the scleral trabeculum may be of importance in this respect. It is seen that when the anterior chamber is large the intertrabecular spaces are wide open (Fig. 4), whereas in the case of a narrow anterior chamber they are close together in a fan-shaped arrangement (Fig. 5).

The importance, in this respect, of the ocular structure in general and of the structure of the iridocorneal angle in particular is indirectly demonstrated by the values obtained by perfusion of a number of myopic eyes. In these eyes the resistance to outflow was manifestly less marked than the normal average resistance (Table 2 and Fig. 6).

Our investigations concerning the depth of the anterior chamber have been confirmed by those of Becker and Constant (1956), who determined the value of *C* in cats (1.54 in vivo and 1.62 in vitro), guinea pigs (0.08 in vivo and 0.09 in vitro), and rabbits (0.35 in vivo and 0.37 in vitro). Comparing the values of outflow (*C*) with the volume of the anterior chamber (*V*), which is apparently proportional to its depth, they found a direct constant relationship, the average *C* value ranging from 1.3 to 1.8 in all animals. They also altered the volume of the anterior chamber in enucleated human eyes, either by applying forceps to the sclerotic or by in-

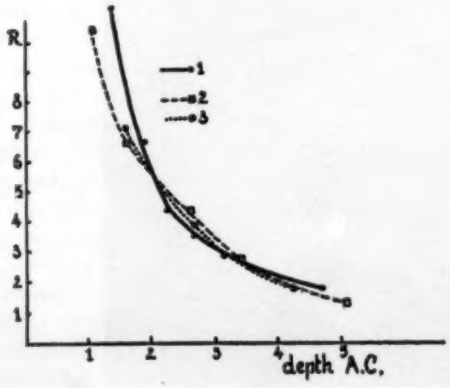

Figure 6

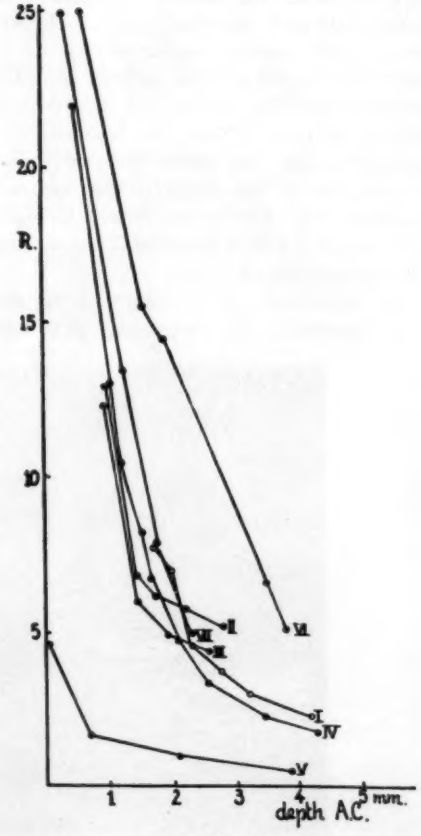

Figure 7

TABLE 3.—*Depth of Anterior Chamber in Pathological Cases*

Case	Depth of Anterior Chamber, Mm.	*R*
I. Retinal glioma	4.25	2.26
	4.05	2.34
	3.2	3.0
	2.8	3.84
	2.3	4.6
	1.95	7.0
	1.7	7.84
II. Right eye of a prematurely born infant (7 mo.) with localized goniosynechia	2.8	5.16
	2.2	5.74
	1.75	6.22
	1.5	6.84
	1.0	13.0
III. Left eye of the above prematurely born infant	2.3	4.4
	1.95	5.0
	1.5	6.0
	1	12.5
IV. Closed-angle glaucoma	5.1	1.8
	4.15	2.3
	3.4	3.3
	2.9	4.8
	2.5	6.7
	2.35	8.3
	2.0	10.5
	1.8	13.0
	1.3	22.0
V. Open-angle glaucoma with iridencleisis	4.7	0.47
	2.9	1
	1.5	1.72
	0.8	4.7
VI. Secondary glaucoma due to rubeosis of the iris	4.6	5.1
	4.3	6.6
	2.7	14.5
	2.4	15.5
	1.4	25.8
VII. Retinal glioma	3.2	4.8
	2.9	5.7
	2.5	7.8
	2.05	13.5
	1.4	25.0
	1.1	36.5

jecting serum into the vitreous body. Like ourselves, they observed a decrease in the facility of outflow with a decrease in volume of the anterior chamber.

The importance of the depth of the anterior chamber has also been confirmed in pathological cases, of which some examples are given in Table 3 (Fig. 7).

II. The Influence of the Tension of the Perfusion Fluid

A study of the influence of the tension of the perfusion fluid on the rate of perfusion is of importance not only theoretically but because the aqueous humor is discharged under increased pressure in the case of glaucoma.

Various papers have been devoted to this question. During perfusion of rabbit eyes Grant (1950) observed that the facility of

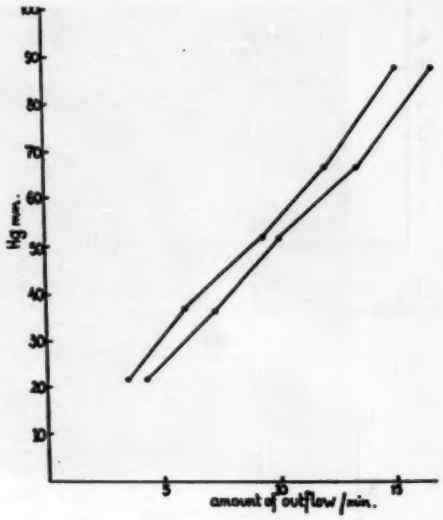

Figure 8

outflow was directly proportional to the tension whenever tension was within the limits of 20 to 60 mm. Hg; during perfusion of bovine eyes Weekers et al. (1956) found a slight increase in resistance with increased tensions. Becker and Constant (1956), studying human subjects, found a constant relationship between the quantity of outflowing fluid and the tension whenever this varied from 20 to 50 mm. Hg.

Thirty-eight human eyes were perfused under pressures varying from 20 to 80 mm. Hg; in the majority of cases (79%) the rate of perfusion was directly and linearly proportional to the tension of the fluid. The resistance to outflow remained unaltered or

TABLE 4.—*Resistance of Outflow with Various Pressures of Perfusion*

	Tension, Mm. Hg	Outflow, Cu. Mm. /Min.	*C*	*R*	*P**
Right eye	22	4.3	0.2	5	3.3
	37	7.3	0.2	5	
	52	10.0	0.19	5.26	
	67	13.3	0.2	5	
	88	16.6	0.19	5.26	
Left eye	22	3.5	0.16	6.25	3.3
	37	6.0	0.16	6.25	
	52	9.4	0.18	5.55	
	67	12.0	0.18	5.55	
	88	15.0	0.17	5.88	3.8

* *P*, depth of anterior chamber, millimeters.

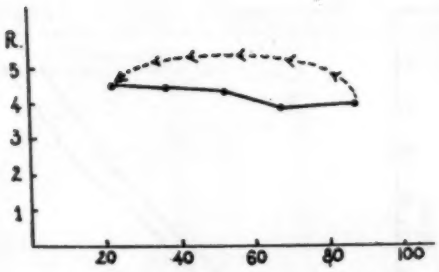

Fig. 9.—The abscissa shows the ocular tension in millimeters of mercury.

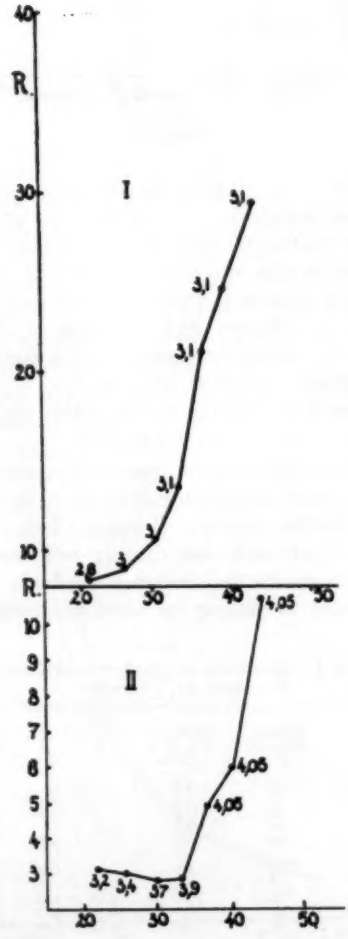

Fig. 10.—The abscissa shows the ocular tension in millimeters of mercury.

TABLE 5.—*Example of Reversibility of* R *Value*

Tension, Mm. Hg	Outflow, Cu. Mm./Min.	C	R	P
22	5.0	0.22	4.5	3.3
37	8.3	0.22	4.5	
52	12.0	0.23	4.3	
67	17.6	0.26	3.8	
88	22.0	0.25	4.0	3.8
20	4.5	0.22	4.5	

slightly increased under pressures varying from 20 to 60-80 mm. Hg. A characteristic example is given in Table 4 (Fig. 8).

As to the relation (direct) between the tension and the quantity of fluid discharged, Grant (1955) concludes that the canaliculi responsible for the resistance to outflow may be capillaries; if orifices were involved there would be a quadratic relationship.

The question may be raised as to whether the perfusion fluid discharged under increased pressure leaves the eye by the same routes as that discharged under normal pressure. India ink did not seem to move faster in the episcleral vessels, and histological examination showed no difference either. We have even gone so far as to make fragments of the iridocorneal angle transparent by treatment with toluene: The impression was gained that the number of efferent vessels visualized by India ink was not increased.

TABLE 6.—*Examples of Nonreversibility of* R *Value*

Case	Tension, Mm. Hg	Outflow, Cu. Mm./Min.	R	P
I	21	2.53	8.30	2.6
	26	2.92	8.90	3
	29.5	2.80	10.55	3
	33	2.43	13.50	3.1
	37	1.78	21.0	3.1
	40	1.62	24.6	3.1
	44	1.50	29.3	3.2
	21	0.45	46.2	2.6
II	22	7.25	3.04	3.2
	26	8.85	2.94	3.4
	29.5	10.8	2.74	3.7
	33	11.8	2.81	3.9
	37	7.7	4.81	4.05
	40	5.55	5.91	4.05
	44	4.12	10.7	4.05
	21	1.08	19.6	3.2
III	100	6.6	15.1	2.4
	20	0.5	40.0	
IV	22	5.5	4	3.8
	30	8.0	3.8	3.8
	44	12.0	3.7	3.8
	60	15.0	4.0	3.8
	74	17.0	4.54	3.8
	88	17.0	5.26	3.8
	20	1.25	16.0	3.8

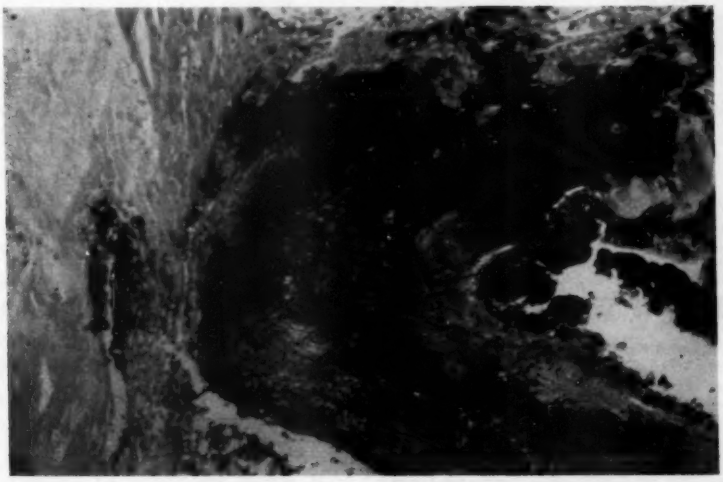

Figure 11

Restoration of the increased pressure to its initial value of 20 mm. Hg is generally followed (in 83% of cases) by an unchanged *R* value or by a slight increase in *R* value as compared with the initial value. There exists, therefore, reversibility. An example is given in Table 5 (Fig. 9).

A linear relationship between the increase in tension and the resistance to outflow is not always found. In some cases the resistance shows a considerable increase to the extent to which the tension of the perfusion fluid increases. In these cases, as in other instances, restoration of the tension to its normal value is not associated with normalization of the resistance (or it returns but very slowly to its initial value); the term reversibility is therefore not applicable here. This fact was particularly clearly demonstrated in four cases (Table 6 and Fig. 10). These cases show that the increase in perfusion pressure can in some cases almost completely block the outflow of the fluid. One of the eyes in question was histologically examined: The base of the iris and the iris itself were pushed back against the trabeculum, which explains the obstruction to outflow, as under these conditions the angle is completely obstructed (Fig. 11). The condition is highly reminiscent of what is seen in closed-angle glaucoma.

On the other hand, there is diminished resistance, as in the case shown in Table 7 (Fig. 12). This fact is generally associated with an increase in the depth of the anterior chamber, which facilitates the aqueous outflow. Yet it is often difficult to maintain a constant depth.

TABLE 7.—*Case of Diminished Resistance with Increase in Depth of Anterior Chamber*

Tension, Mm. Hg	Outflow, Cu. Mm./Min.	*R*	*P*
22	4.4	5.0	3.6
26	6.0	4.35	3.9
29.5	6.1	4.8	3.9
37	7.7	4.82	4.0
44	24.0	1.84	4.35
22	3.22	6.80	3.5

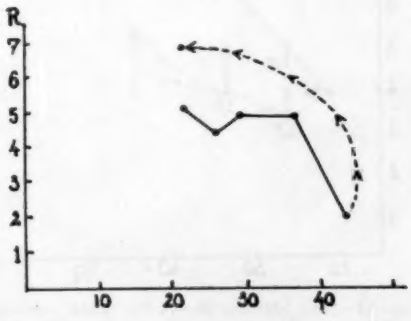

Fig. 12.—The abscissa shows the ocular tension in millimeters of mercury.

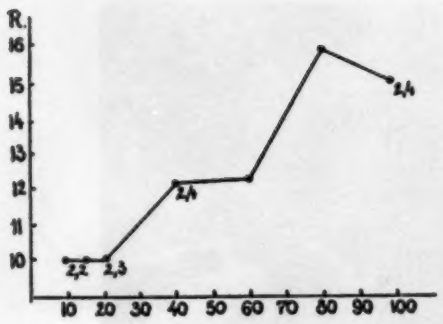

Fig. 13.—The abscissa shows the ocular tension in millimeters of mercury. The numbers by each dot indicate the depth of the anterior chamber in millimeters.

The linear relationship between the perfusion pressure and the resistance is found only when experiments involve eyes with a wide anterior chamber; this becomes deeper as a result of the increase in pressure, which facilitates the aqueous flow.

If the same experiments are made with the depth of the anterior chamber kept constant or with eyes having a narrow anterior chamber, then there is nearly always an increase in resistance to increased pressure. An example is given in Table 8 (Fig. 13).

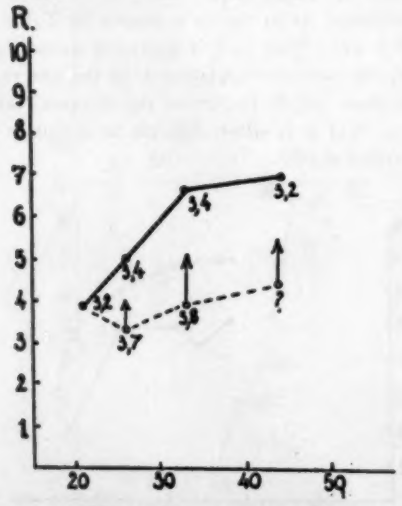

Fig. 14.—The abscissa shows the ocular tension in millimeters of mercury. The numbers by each dot indicate the depth of the anterior chamber in millimeters.

TABLE 8.—*Increase of Resistance with Increase of Pressure in a Case with Constant Narrow Anterior Chamber*

Tension, Mm. Hg	Outflow, Cu. Mm./Min.	*R*	*P*
10	1.0	10.0	2.2
15	1.54	10.0	
20	2.0	10.0	2.3
40	3.3	12.2	2.4
60	5.0	12.2	
80	5.0	16.0	
100	6.6	15.1	2.4

Every time that, after an increase in depth of the anterior chamber due to increased pressure, the chamber is restored to its initial depth, the resistance is seen to increase. This experiment has been made in six cases, of which an example is given in Table 9 (Fig. 14).

It seems justifiable to conclude that, although an increase in tension in the anterior chamber generally does not alter the facility of outflow, this increase may more or less markedly slow down the outflow, especially when the anterior chamber is not very deep. This slowing down is also due, apparently, to a change in the iridocorneal angle.

Conclusions

The narrower the anterior chamber the more the facility of outflow is reduced and vice versa. This fact can be verified not only in normal eyes but also in eyes pathologically affected.

The *C* and *R* values obtained in vivo (tonography) or in vitro (perfusion) should be considered, in order to allow of comparison, as a function of the depth of the anterior chamber.

The change in facility of outflow associated with a change in depth of the anterior chamber is probably based on a change in trabecular structure.

TABLE 9.—*Increase in Resistance When Anterior Chamber, After Increase in Depth, is Restored to Its Initial Depth*

Tension, Mm. Hg	Outflow, Cu. Mm. /Min.	*R*	*P*	Constant *P*	Outflow, Cu. Mm. /Min.	*R*
21	5.45	3.84	3.2			
26	7.88	3.30	3.7	3.4	5.20	5.0
33	8.35	3.96	3.8	3.2	5.0	6.60
44	10.0	4.40	?	3.2	6.32	6.95

The rate of perfusion is as a rule directly and linearly proportional to the tension of the fluid, and so the resistance to outflow is not or is only slightly altered.

Restoration of an increased tension to the initial value of 20 mm. Hg generally shows *C* and *R* values more or less the same as at the onset of the experiment, which demonstrates reversibility.

There are nevertheless cases in which the resistance either increases or decreases when the tension of the perfusion fluid is increased or restored to its initial value.

2 Avenue Pasteur.

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Agar Microelectrophoresis of the Aqueous Humor

J. FRANÇOIS, M.D.; M. RABAEY, M.D., and L. EVENS, M.D., Ghent, Belgium

Electrophoretic determination of protein values in normal aqueous humor offers considerable difficulties, owing to the following two factors: Proteins are present only in minute quantities, whereas there are considerable quantities of salts as against the low protein concentration.

I. The Minute Protein Quantities

The aqueous humor normally contains 10 to 40 mg. of total protein per 100 ml., i. e., 10μg. to 40μg/100μl. (microliters), according to Amsler, Verrey, and Huber (1955).

Paper electrophoretic examination of blood serum under favorable conditions generally requires 10μl. (600 to 800μg. of protein). Quantities of less than 5μl. yield no reliable results, as shown by the investigations of Klatskin, Reinmuth, and Barnes (1956), who made a critical analysis of quantitative-fractional paper electrophoresis of blood proteins, and by our personal observations.

If the protein solution is deposited on the paper at one localized point rather than in a line, then the serum quantity required can be reduced four times; however, 100μg. of protein is still required.

Now, the quantity of aqueous humor usually obtained by puncture of the anterior chamber is about 150μl., which corresponds to 15μg. to 45μg. of protein!

Filter paper electrophoretic assays of protein fractions in the aqueous humor have nonetheless been made by various investigators. These assays may be successful if the aqueous humor used is pathological or of the secondary type, in which the protein level is mostly increased (Witmer, 1952; Wunderly and Cagianut, 1952; Esser, Heinzler, and Pau, 1954).

With normal aqueous humor certain authors circumvented this difficulty by adding several different aqueous humors. (*a*) Esser, Heinzler, and Pau (1954) added the results of 11 chamber punctures and compared the values obtained with those obtained in serum and in CSF. Their findings are presented in Table 1. (*b*) Wunderly, Steiger, and Böhringer (1954) added two or three aqueous humors and likewise compared the results with those obtained in serum and in CSF (Table 2). (*c*) D'Ermo (1955) succeeded in protein electrophoresis in a single sample of aqueous humor (150μl.) concentrated by evaporation on cellophane. His results are as follows: albumin, 60%; α_1-globulin, 6.45%; α_2-globulin, 11.48%; β-globulin, 8.92%; γ-globulin, 13.45%.

Regardless of the merits of these attempts, it can be stated that the quantity of protein made available by a single puncture of the anterior chamber is so small as to remain outside the limits of possibility of paper electrophoresis, of which the results—under

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TABLE 1.—*Results of Esser, Heinzler, and Pau* [1]

	Electrophoretic Fraction, %					
	Prealbumin	Albumin	α_1-Globulin	α_2-Globulin	β-Globulin	γ-Globulin
Aqueous humor	0.6	64.9	4.8	7.1	18.5	4.1
Serum	--	59.0	4.3	7.7	12.5	16.5
CSF	1.2	56.1	4.7	7.5	24.1	6.4

TABLE 2.—*Results of Wunderly, Steiger, and Böhringer* [13]

	Albumin, %	α-Globulin, %	β-Globulin, %	γ-Globulin, %
Aqueous humor (mean value)	62.6	9.2	10.4	17.4
Human serum	59.1	8.8	13.8	18.3
CSF	59.6	12.8	19.0	9.8

these conditions—are questionable (Goodner, 1956).

II. The Considerable Quantity of Salts as Against the Low Protein Concentration

A satisfactory electrophoretic determination can only be made if the protein level of the aqueous humor is sufficiently increased; hence the necessity of fifty- to one-hundredfold concentration of the latter. As a result of this concentration, the salt level, which is normally about 1%, increases to enormous proportions; consequently, not only is the course of electrophoresis unfavorably influenced but even a sufficient concentration is made impossible unless the majority of the salts are eliminated.

To concentrate the aqueous humor obtained, Wunderly, Steiger, and Böhringer (1954) and D'Ermo (1955) resorted to evaporation to 10% of the original volume; Esser, Heinzler, and Pau (1954) used dialysis under pressure, and Bücher, Matzelt, and Pette (1952) used precipitation. The last-mentioned investigators, examining the CSF, caused precipitation of soluble proteins at 0 C by addition of acetone; after centrifugation the precipitate was redissolved in a small quantity of fluid.

Both dialysis under pressure and precipitation are difficult to apply to aqueous humor, as the quantity available as a rule does not exceed 150μl. We have used the following procedure.

1. *Elimination of Salts.*—First the salts are eliminated from the aqueous humor by dialysis against a diluted barbital (Veronal) sodium buffer solution.* The dialysis is made either in the dialyzer of Kern's electrophoretic apparatus or in a small dialyzer of our own design. Both dialysis and transportation of the fluid can be effected practically without any loss if capillary pipets are used.

2. *Concentration.*—The dialyzed aqueous humor is then concentrated by lyophilization or by evaporation.

(*a*) Lyophilization (freeze drying) is the technique of choice. The fluid is dried in a capillary pipet at about −15 C. The dry substance thus obtained is then dissolved in 2μl. of water and introduced into the agar.

(*b*) A simple technique which ensures considerably less marked loss of substance consists of aspiration of dialyzed aqueous humor in a capillary pipet of 100μl. capacity, with a flat end on which a small piece of filter paper (1×2 mm. or 1×1 mm.) is then placed. The water which soaks the filter paper is evaporated as imbibition proceeds, with the aid of a ventilator. The pipet is gradually emptied, and the proteins meanwhile concentrate on the filter paper. A few (two to six) hours are sufficient to concentrate 100μl.; manipulations should be done at a low temperature if possible.

Subsequently it is extremely simple to introduce the small piece of filter paper into the agar, after which electrophoresis is started. Although the crack made in the agar at the site of introduction of the filter paper may be larger than that caused by the introduction of fluids, these two methods have always yielded identical results, both in aqueous humor and in blood serum investigations.

Electrophoresis

As to electrophoresis itself, it has been established that paper electrophoresis is unsuitable for the study of minute protein quantities; we therefore have had to resort to other methods, among them microelectrophoresis. The sensitivity of the latter method is dependent on and limited by the sensitivity of protein-staining techniques. This sensitivity, however, cannot be increased at the present time.

* Composition of the dialysis fluid: barbital sodium, 8.5 gm.; normal hydrochloric acid, 11 ml.; distilled water, 500 ml.; 2% to 10% of this solution is used, according to the protein level of the aqueous humor.

There is still another possibility. A protein solution deposited on a filter paper spreads over a relatively large area, and so the fractions are rather large, especially since diffusion increases in the course of prolonged electrophoresis. The width of the serum protein fractions measures at least 1 cm.

If, on the other hand, electrophoretic determinations could be made in such a manner that the solution to be analyzed is applied over a very small area, and so that diffusion is minimal, then it would be possible, even with very small quantities of protein, to maintain a sufficiently high concentration in connection with the staining technique. In other words, the field covered by electrophoresis should be reduced.

From this point of view, electrophoresis on agar has considerable advantages. If the appropriate technique is used, the width of the bands corresponding with the various protein fractions can be reduced to 1 mm., which ensures a one-hundred-fold enhancement of sensitivity.

Technique of Electrophoresis on Agar (Wieme and Rabaey, 1957).—Liquefied, heated agar † is poured onto a small glass disc or a microscope slide in such a way as to obtain a layer of 1.5 to 2 mm. The agar is allowed to solidify and to cool, after which the protein solution is introduced, with the aid of a capillary pipet, into a small excavation or, if the quantity of fluid is sufficient, into a small linear groove cut in the agar. This introduction is best done with the aid of a binocular microscope. The use of the linear groove is preferable because it ensures more exact quantitative estimation.

Electrophoresis requires 10 to 30 minutes, with use of a constant current of 8 to 12 ma. for each slide. After completion of electrophoresis the agar plate is fixed ‡ for at least 30 minutes. During fixation the protein fractions gradually become visible in the form of opaque spots or bands.

† Dry agar (Bacto-Agar, Difco), 1.25%, in a buffer solution with barbital sodium, pH 8.4, ionic strength 0.05.

‡ Fixation fluid: 5% acetic acid in 70% ethanol.

The slide is then covered again with a piece of filter paper and dried at 37 C. After this it can be treated as a microscopic preparation. It is stained for 30 minutes in an amido black solution § and then washed in acid solution ‖ until the agar background is completely decolorized throughout. The slide is then again dried, rendered transparent in toluene, and mounted in Harleco synthetic resin.

The protein pattern is quantitatively read with the aid of a sensitive densimeter. The image of the slide, enlarged 20 times, is projected into a depolarized glass bearing a slit diaphragm measuring 2 mm. and a very precise photoelectric cell (Photomultiplier R. C. A. 931). The densities are plotted against the migration on millimeter-ruled paper. The density curves are then integrated with the aid of planimetry or by weighing the zones cut below the apex.

Investigations

Various investigations were made in order to determine the value of this method.

I. Normal human serum was diluted, dialyzed, and treated in the same way as was the aqueous humor; normal and treated serum samples were then simultaneously submitted to electrophoresis on the same slide (Fig. 1).

Electrophoresis of normal human serum on agar made it possible to separate albumin, α-globulin, β-globulin, and γ-globulin. Three aspects should be especially mentioned.

(*a*) Two prealbumin fractions were seen in front of the albumin. One of these was inconsistent and seemed to move with difficulty in the agar, in which it formed a trail. The other fraction, the prealbumin proper, was as a rule much less marked and migrated slightly farther. It should be pointed out that these prealbumin fractions were not seen after paper electrophoresis.

§ Staining material: amido black 10 B, 0.5 gm.; mercuric chloride, 5 gm.; acetic acid, 5 ml.; distilled water, 95 ml. (filter before use).

‖ Five per cent acetic acid in distilled water.

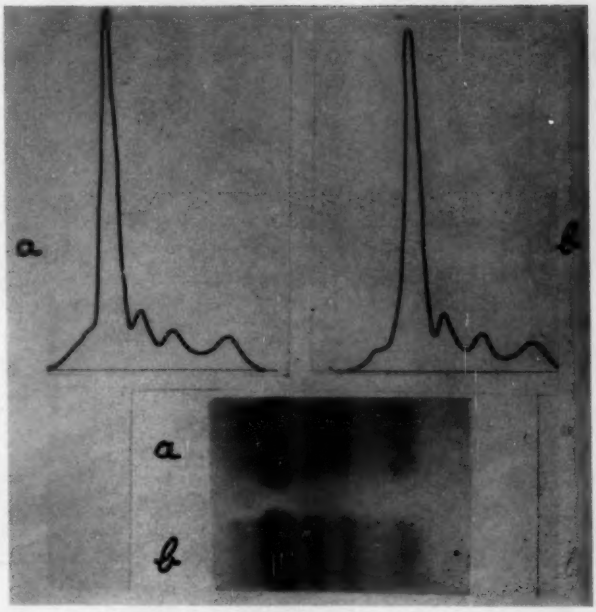


Fig. 1.—Diagram of an electrophoretic determination on agar in a sample of normal human serum. (*a*) Control; (*b*) after treatment identical to that applied to aqueous humor.

(*b*) Electrophoresis on agar was unable to separate α_1-globulin from albumin.

(*c*) Differences from paper electrophoresis were particularly marked in β-globulin and γ-globulin values obtained. Table 3 first gives the values obtained by agar electrophoresis with normal serum and then, the values obtained with the same untreated serum (control) and with the same serum treated as was described for aqueous humor.

An immediately striking feature was that the values obtained in human serum were markedly different from those obtained by paper electrophoresis. The albumin percentage was much higher, and the β-globulin and γ-globulin values were much lower. The γ-globulins in particular showed much higher values on paper (20% to 30% in some laboratories). If one takes into account the correcting factor as to stain absorption, however, values of β-globulin and γ-globulin fractions correspond well with those obtained by free electrophoresis.

TABLE 3.—*Results of Agar Electrophoresis of Serum*

	Prealbumin, %	Albumin, %	α-Globulin, %	β-Globulin, %	γ-Globulin, %
Normal serum	3.3	67.7	9.7	8.3	11
Untreated serum	6.9	63.0	10.5	8.3	11.3
Serum treated as aqueous humor	5.3	64.6	11.2	7.9	11

A recent critical analysis made by Klatskin et al. (1956) showed that such satisfactory percentages of the various protein fractions obtained by paper electrophoresis must be regarded as unexpected. Paper electrophoresis is actually subject to a series of causes of error which have for the most part been neutralized by coincidence. Values obtained by paper electrophoresis can only be compared, moreover, when about the same quantity of protein has been used each time. The values obtained by agar electrophoresis are more independent of the quantity of protein used in determination.

Comparison between the nontreated and the treated serum, as was done with aqueous humor, shows the same percentages of the various fractions.

II. Similar investigations were made with use of normal human CSF. In Table 4 the average values of the various protein fractions in the CSF are first given according

TABLE 4.—*Results of Agar Electrophoresis of CSF*

	Prealbumin, %	Albumin, %	α-Globulin, %	β-Globulin, %	γ-Fraction, %	γ-Globulin, %
Mean normal values	4.4	49.7	15.4	11.5	8	11
Treated CSF (paper electrophoresis)	4.7	51.5	12.0	13.7	8.1	9.8
Untreated CSF (agar electrophoresis)	6.2	71.2	6.1	7.5	3.6	5.4

to the findings of Bücher, Matzelt, and Pette (1952), obtained by paper electrophoresis. The second line shows the CSF protein fractions after treatment similar to that described above for aqueous humor; all these values were obtained by paper electrophoresis (Fig. 2,*a*). The final line shows the values obtained by agar electrophoresis in another sample of human CSF (Fig. 2,*b*).

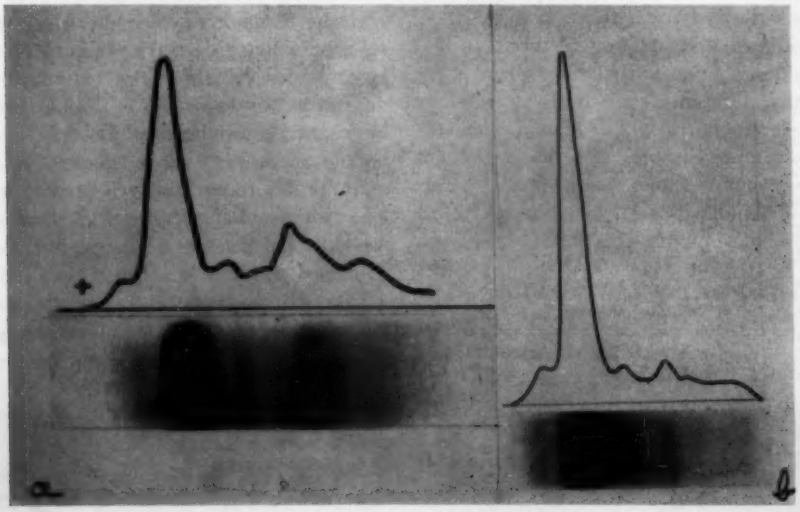
The β-globulin and γ-globulin fraction values obtained by agar electrophoresis were considerably lower than corresponding values obtained by paper electrophoresis. As to the α-globulin fraction, the value obtained by agar electrophoresis represents only the α_2-globulin fraction, whereas that obtained by paper electrophoresis represents the sum of the α_1- and the α_2-globulin fractions. It should be borne in mind that agar electrophoresis does not permit of differentiation between the α_1-globulin and the albumin fraction.

III. A fairly large quantity of bovine aqueous humor was treated and concentrated by the technique described. The results obtained by agar and paper electrophoresis of this fluid were compared with those obtained with normal bovine serum (Figs. 3 and 4).

Both paper and agar electrophoresis with bovine material show an increase in β-globulin value in the aqueous humor and a decrease in γ-globulin. The latter decrease is relatively less marked in paper electrophoresis than in agar electrophoresis. This is largely due to the fact that, in paper electrophoresis, the error due to elevation of the base line of γ-globulins, which is very extensive, is larger to the extent to which the γ-globulin concentration is lower.

IV. An attempt was finally made to verify our staining method and our method of quantitative analysis. We prepared a series of solutions of pure γ-globulin and pure albumin in almost equal concentrations.

Fig. 2.—(*a*) Paper electrophoresis and diagram of human CSF treated as aqueous humor. (*b*) Agar electrophoresis and diagram of human CSF treated as aqueous humor.



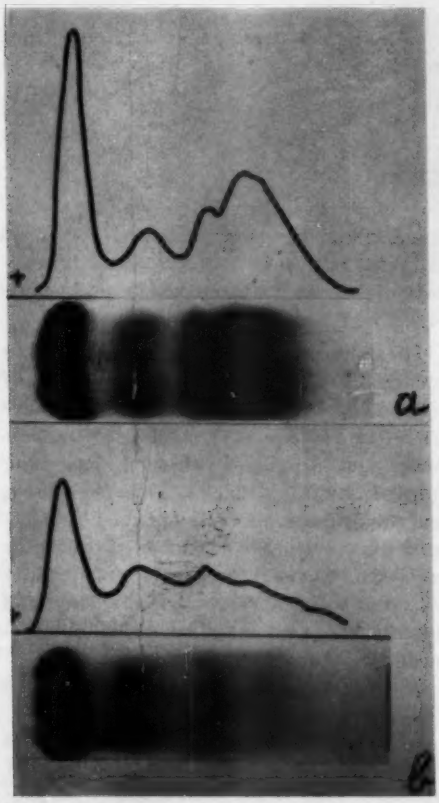


Fig. 3.—Paper electrophoresis and diagram of bovine serum (*a*) and bovine aqueous humor (*b*).

The concentration of each of the isolated proteins was determined by weighing the dry substance. Several dilutions were made of this solution so as to obtain 10 different solutions with an albumin or γ-globulin concentration varying from 0.02% to 3.5%. Each of these solutions was used in agar electrophoresis, and each time the same quantity was introduced over a length of 5 mm. All electrophoretic determinations were made twice. The slides were simultaneously dried, stained, and washed, after which the results were read on the densimeter. The total curve densities of both the albumin and the γ-globulin were plotted against the protein quantities used (Fig. 5). In both cases we obtained a linear relationship, although it was necessary to use the entire length of the galvanometer gradation (Fig. 5).

In this manner it was possible to determine that the total density of the γ-globulin fraction was much lower than that of the albumin, which shows that the γ-globulin fraction absorbs considerably less of the staining matter than albumin. The γ-globulin value obtained had to be multiplied by a correction factor equivalent to 1.85.

It was thus established that different proteins differ considerably as to absorption of

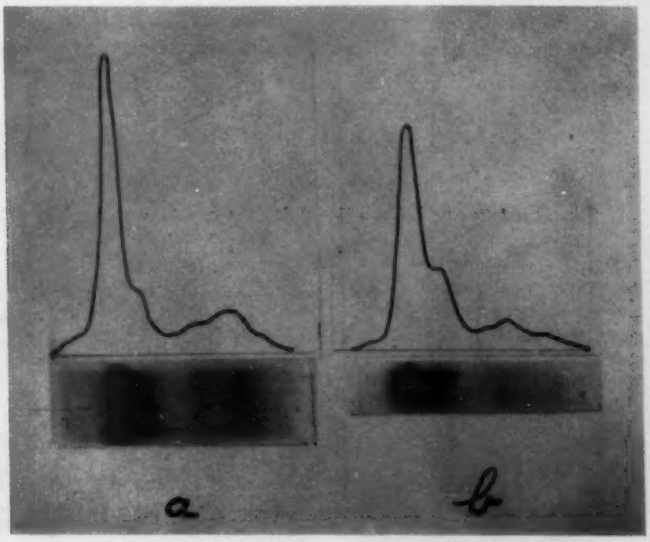


Fig. 4.—Agar electrophoresis and diagram of bovine serum (*a*) and bovine aqueous humor (*b*).

TABLE 5.—*Results of Electrophoresis of Bovine Serum and Aqueous Humor*

	Prealbumin, %	Albumin, %	α-Globulin, %	β-Globulin, %	γ-Globulin, %
Paper electrophoresis					
Serum		37.5	13.4	11.1	37.9
Aqueous humor		40.2	24	15.8	19.9
Agar electrophoresis					
Serum	3.5	57.5	11.9	8.35	18.7
Aqueous humor	1.6	58.7	23.4	10.3	6.2

staining matter—a fact previously demonstrated by Loeffler and Wunderly (1953); Mackay, Volwiler, and Goldsworthy (1954), and Jencks, Jetton, and Durrum (1955). In the case of paper electrophoresis this difference is generally compensated by other flaws inherent in the method.

The results given above for normal serum clearly show that the β-globulin and γ-globulin values are lower than those obtained by free electrophoresis according to Tiselius.

We did not determine the correction factors for human β- and γ-globulin. The correction factor 1.85 to 2 gives values for the two fractions which are comparable to those obtained by free electrophoresis.

Again we should like to emphasize the unfavorable effect of differences in stain absorption. The γ-globulin fraction, which has a relatively low stain absorption, is found in low concentrations in the aqueous humor. Also it is necessary, if the exact proportion of this fraction is to be established, to introduce into the agar a sufficiently large quantity of proteins to ensure an excessively high albumin apex. Under the circumstances it is useful to develop a staining method in which the albumin fraction is bound to absorb a relatively small quantity of staining matter. This problem is being investigated.

In summary, it can be stated that our method of concentrating and our method of microelectrophoresis on agar make it possible to ensure suitable fractionation of proteins in the aqueous humor with very small quantities of fluid; 25μl. to 80μl. as a rule suffices, and the quantity normally obtained by puncture of the anterior chamber is therefore ample for this purpose, leaving a quantity of fluid sufficient for albumin assay and microscopic examination of the cellular elements.

Comment

In studying proteins in normal aqueous humor, two questions should first be considered: What is the total quantity of proteins present, and what are the various protein fractions and their percentual values?

Such samples of aqueous humor as were examined were obtained by in vivo puncture

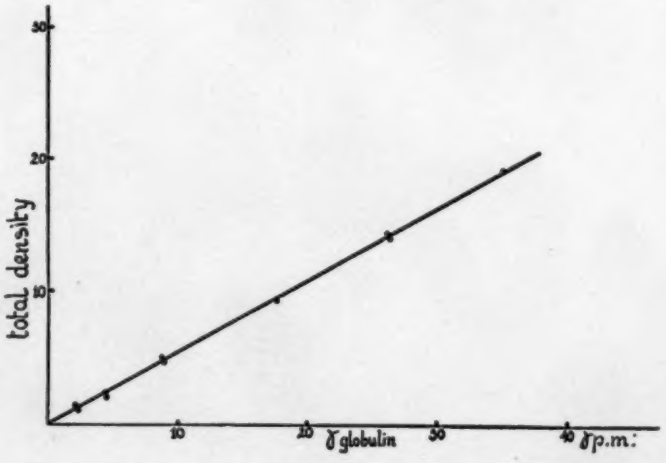


Fig. 5.—Relation between the total density and the bovine γ-globulin concentration after agar electrophoresis and amido black staining.

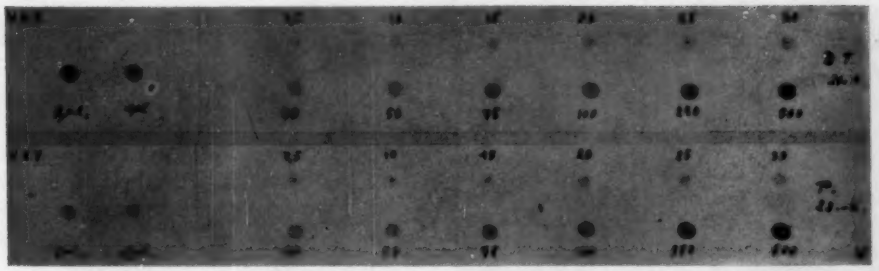


Fig. 6.—Determination of the protein quantity in two specimens of aqueous humor. Left, aqueous humor to be examined. Right, various dilutions of blood serum; figures indicate protein quantity in milligrams per 100 ml.

of the anterior chamber or by puncture of the anterior chamber as soon after death as possible, as a rule within two hours. Examination of aqueous humor obtained in vivo was always combined with serum electrophoresis.

I. Total Protein Quantity in the Aqueous Humor.—The protein concentration of the aqueous humor was determined by a method analogous to that of Wunderly, Steiger, and Böhringer (1954). Although this method may not be characterized by great precision, it gives approximate values which are in any case sufficient to determine the extent to which the humor must be concentrated to ensure electrophoresis under optimal conditions.

We have used bands of filter paper (Schleicher & Schüll, No. 2043 Mgl.) on which we deposited a drop of serum protein in different concentrations, varying from 7.5 to 500 mg/100 ml. At the end of the band we deposited $1\times1\mu$l. or $2\times1\mu$l. of aqueous humor. The band was dried and stained, as is also done for paper electrophoresis. Comparison between the spots of aqueous humor

Fig. 7.—Left, serum diagram; right, aqueous humor diagram. Figures correspond with case numbers in Table 6.

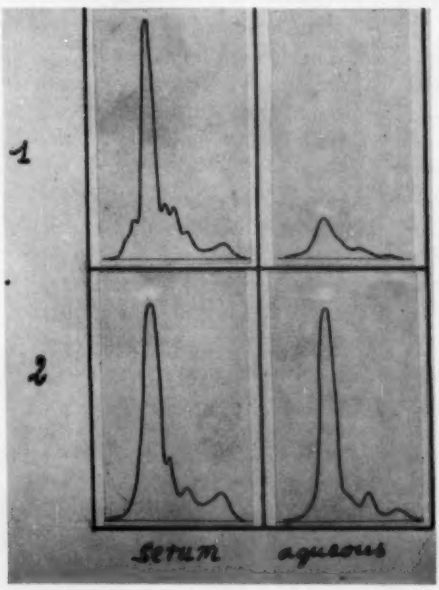
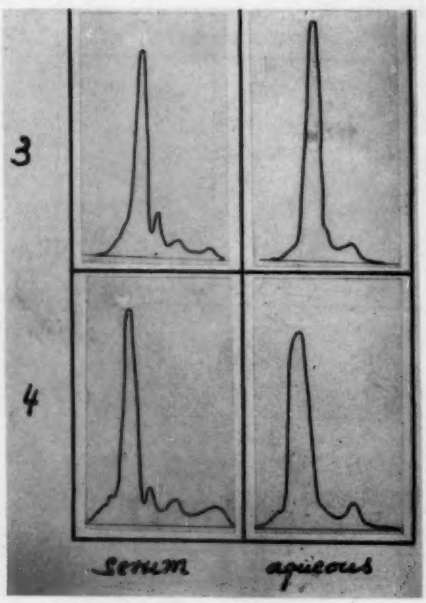


Fig. 8.—Left, serum diagram; right, aqueous humor diagram. Figures correspond with case numbers in Table 6.



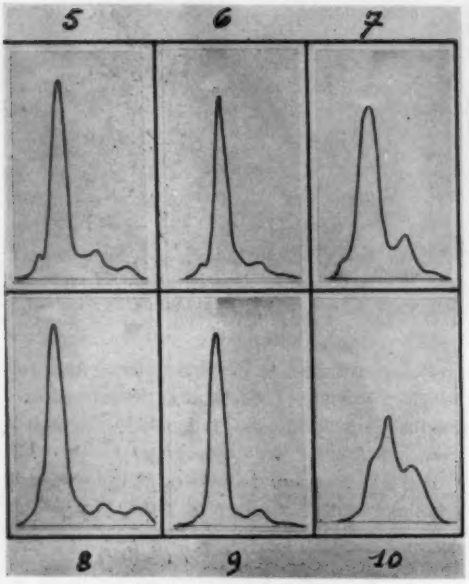


Fig. 9.—Various aqueous humor diagrams. Figures correspond with case numbers in Table 6.

and those of serum makes it possible to obtain an approximate estimate of the protein concentration in the aqueous humor (Fig. 6).

Fig. 10.—Various aqueous humor diagrams. Figures correspond with case numbers in Table 6.

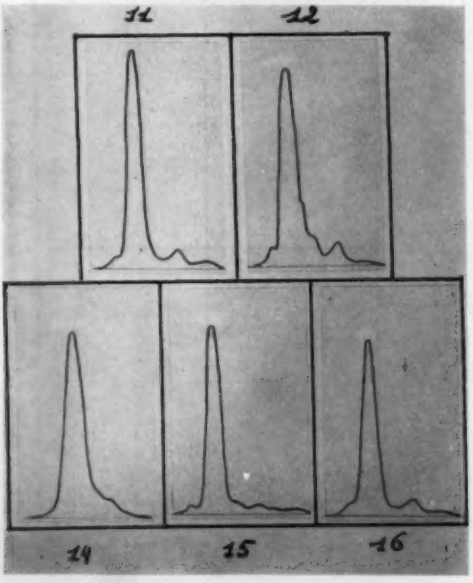


TABLE 6.—*Results of Electrophoresis of Human Serum and Aqueous Humor*

Case	Age, Yr.	Material	Total Protein, Mg./100 Ml.	Prealbumin, %	Albumin, %	α-Globulin, %	β-Globulin, %	γ-Globulin, %	Remarks	Figure in Text
1	2 1/2	Serum		7.8	64.1	15.3	5.9	6.9	Normal eye; increased γ globulin	7
		Aq. hum.	<10	3.2	66.5	14.3	12.3	3.6		
2	36	Serum		3.3	67.8	9.7	8.3	11.0	Previous detachment	7
		Aq. hum.	250	3.8	77.7	5.9	7.6	4.9	Cataract	
3	67	Serum		6.9	70.0	11.5	6.4	5.3	Detachment; increased α-globulin	8
		Aq. hum.	40	3.1	85.3	3.2	7.8	0.6		
4	65	Serum		7.3	63.8	7.6	9.6	11.1	Choroid sarcoma	8
		Aq. hum.	100	3.6	81.8	4.3	8.1	2.2		
5	66	Aq. hum.	100	4.7	73.4	6.1	9.7	6.0	Cadaver	9
6	58	Aq. hum.	100	4.9	74.7	9.4	8.1	2.8	Cadaver	9
7	49	Aq. hum.	15	2.4	74.9	5.4	15.2	2.1	Cadaver	9
8	80	Aq. hum.	150*	7.6	70.5	4.9	7.6	7.0	Fraction Gr. 20 + 2.3%; cadaver	9
9	43	Aq. hum.	40	2.8	84.8	3.6	7.7	1.6	Cadaver	9
10	43	Aq. hum.	25	1.2	23.5	44.9	30.0	...	Death due to eclampsia	
11	70	Aq. hum.	80	3.0	82.3	3.6	6.8	4.3	Cadaver	10
12	75	Aq. hum.	50	3.9	77.3	7.8	8.5	2.4	Cadaver	10
13	72	Aq. hum.	20*	0.9	85.3	7.0	5.4	1.4	Cadaver	10
14	73	Aq. hum.	80	2.9	85.6	4.0	4.5	3.0	Cadaver	10
15	44	Aq. hum.	25	4.1	80.9	3.6	8.0	3.3	Cadaver	10

* See Figure 7.

In about 50% of cases the values obtained were higher ($\leqq$50 mg.) than those considered normal in general. On the other hand, they have been shown to be very variable, ranging from 10 to 150 mg/100 ml. We also had the impression that the protein level of the aqueous humor is considerably lower in young than in older subjects. All the results obtained are shown in Table 6.

II. Distribution of the Different Protein Fractions in Normal Aqueous Humor.— Although the results so far obtained do not permit definite conclusions, the following facts have come to the fore.

1. As compared with the serum the aqueous humor shows an increase in albumin and a decrease, more or less marked, in the γ-globulin fraction.

2. A prealbumin fraction is more or less regularly seen, in highly variable concentrations. It can be compared with that in the CSF but not with that revealed by agar electrophoresis of normal serum.

3. The α-globulin concentrations in aqueous humor is variable. It may be either higher or lower than that in the serum.

4. The most constant globulin fraction is the β-globulin fraction, which shows about the same percentage in aqueous humor as in the serum.

5. The γ-globulin percentage is the lowest in those cases in which the total protein level is also low. As this level increases (Case 2) the γ-globulin values approach those of the serum.

6. Case 10 shows a very abnormal protein pattern, which is difficult to explain. Since the eyes were completely normal, it may be supposed that certain causes of a general nature (e. g., eclampsia) may cause considerable changes in the aqueous humor.

A comparison between the values obtained and those reported by Esser, Heinzler, and Pau (1954) shows satisfactory correspondence. No such correspondence is seen when a comparison is made with those obtained by Wunderly, Steiger, and Böhringer (1954) and those of D'Ermo (1955), who found almost identical values for aqueous humor and serum values. A more detailed examination of the curves presented by D'Ermo, however, shows that they are not very different from ours, and that they do not correspond with the figures presented by D'Ermo.

The preliminary results show that electrophoresis, both of normal aqueous humor and of pathological aqueous humor, should be continued, as it is interesting to verify whether certain general affections can in fact influence the protein content of the aqueous humor in apparently normal eyes.

Summary

A new technique is described of quantitative ultramicroelectrophoresis on agar, which makes it possible to analyze a protein quantity of less than 1μl., revealing a minute quantity of protein of about 0.1μg. This technique can be used in fractionation of proteins of the aqueous humor. A single puncture of the anterior chamber furnishes 100μl. to 150μl.; 25μl. to 80μl. is required for agar electrophoresis, and this leaves a sufficient quantity of fluid for albumin assay and morphological examination.

A description is given of the first results, obtained partly with normal human aqueous humor.

2 Avenue Pasteur.

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Dialysis of the Aqueous Against Plasma

RALPH Z. LEVENE, M.D., New York

The demonstration that the electrochemical potential of a substance in the aqueous is greater than the requirements predicted by membrane equilibrium is evidence of an active transport mechanism for the substance. The main difficulty in applying this criterion is the uncertainty of the theoretical requirements. To overcome this difficulty Duke-Elder et al.[1] utilized the technique of direct dialysis of the two fluids against each other. By dialysis, these investigators demonstrated a transfer of sodium from aqueous to plasma, supporting the view that an excess of sodium is present in the aqueous. The present investigation was undertaken as a further study of aqueous-to-plasma dialysis.

Method

Adult male albino rabbits weighing from 2.5 to 3.5 kg. were utilized, and each eye was used only once for aqueous puncture. They were allowed food (Wayne Rabbit Pellets) and water without restriction. Twenty-four hours before use they were transferred from the regular animal room to an air-conditioned laboratory, where all experimental procedures were ultimately carried out.

All procedures were carried out on the restrained conscious animal, with use of topical tetracaine (pontocaine) anesthesia. Blood samples were obtained with a heparinized syringe by cardiac puncture and were immediately centrifuged anaerobically. All syringes were lightly coated with a silicone lubricant to minimize evaporation and carbon dioxide loss.

The method of Duke-Elder et al.[1] for aqueous-to-plasma dialysis was modified for the present study. A cellulose membrane was substituted for the collodion membrane, and the present dialysis apparatus was designed for a plasma volume 10 times that of the aqueous, in contrast to the use of equal volumes of the two fluids in the original study. For each experiment, the aqueous and plasma of seven rabbits were pooled in proportion and 1.5 ml. of aqueous was used for the dialysis. Before the apparatus was sealed with wax, alveolar air was introduced. The dialysis tube was then rocked at a rate of seven cycles per minute at room temperature for four to five hours. A preliminary study with saline and distilled water indicated that this was ample time for equilibration. Other portions of the pooled fluids were used for controls.

Sodium and potassium determinations were made with a standard flame photometer. The instrument error was determined by a comparison of the results from sample pairs of a standard solution in the normal range. For sodium the mean absolute difference between members of each pair was 0.8% of the mean standard value for 12 pairs. For potassium the mean difference was 1.1% of the standard value for an equal number of pairs. Freezing-point depressions were determined with the Fiske osmometer, with use of a 0.2 ml. sample. Three readings of each sample were obtained within two to three minutes. The instrument error was determined as for the flame photometer, and the mean differ-

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From the Department of Ophthalmology, New York University Post-Graduate Medical School.

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TABLE 1.—*Sodium Concentrations*

	Sodium Concentrations, mM./Kg. Water							
	Control			Dialysis			Cont.—Dial.	
Expt. No.	Aq.	Pl.	Aq./Pl.	Aq.	Pl.	Aq./Pl.	Aq.	Pl.
1	141.1	146.9	0.960	136.7	142.9	0.957	+4.4	+4.0
2	136.7	142.3	0.961	135.1	142.9	0.945	+1.6	−0.6
3	144.3	149.8	0.963	139.8	149.8	0.933	+4.5	0.0
4	142.8	144.8	0.986	138.9	143.5	0.968	+3.9	+1.3
5	146.9	147.0	0.999	139.5	147.6	0.945	+7.4	−0.6
Mean	142.4	146.2	0.974	138.0	145.3	0.950	+4.4	+0.8

ence between members of eight pairs was 0.5% of the mean standard value. According to Meschia and Barron,[6] the error from carbon dioxide loss is negligible. Osmolal concentrations were calculated with osmotic coefficients based on the freezing-point data of International Critical Tables[8] and a cryoscopic value for water of 1.86. As Smith[7] has pointed out, these osmotic coefficients refer to osmotic activities at 0 to −2 C and not at 37.5 C. If the activity is temperature-dependent, the present coefficients must be used with reservation.

Concentrations are expressed as millimoles (mM.) or milliosmoles (mOsm.) per kilogram of water, assuming a 7% solid content for plasma and a negligible content for aqueous.

Results

The results of the dialysis experiments are presented in Tables 1, 2, and 3. As the plasma volume within the dialysis apparatus was 10 times that of the aqueous, changes in concentration following dialysis are evident primarily in the aqueous. There was a consistent transfer of sodium from aqueous to plasma of approximately 4.4 mM., similar to the results of Duke-Elder et al.[1] for the dog and cat.

Despite this aqueous loss of sodium following dialysis, there was no associated lowering of the aqueous osmolal concentration. Both fluids showed a slight increase following dialysis. In view of the possibility of an artifact error in osmolal determinations of fluids exposed to room temperature for several hours, a comparison was made of plasma values immediately following cardiac puncture and after they had stood at room temperature for five hours. Exposure to room temperature resulted in a mean increase of 3 mOsm. in four experiments, confirming Kinsey's observations with the thermoelectric vapor-pressure method.[4] As a loss of 4.4 mM. of sodium is equivalent to a loss of 8.1 mOsm., the results cannot be attributed to an artifact error. Thus, the aqueous excess of sodium above membrane equilibrium is to a large extent osmotically balanced by an associated aqueous deficiency of other substances. As Duke-Elder et al.[1] have demonstrated a lowering of the aqueous electrical conductivity following dialysis, the deficiencies are predominantly nonelectrolytes. Analysis of steady-state aqueous and plasma nonelectrolytes has revealed an aqueous deficiency of such substances as urea and glucose.[5]

TABLE 2.—*Osmolal Concentrations*

	Osmolal Concentrations, mOsm./Kg. Water							
	Control			Dialysis			Cont.—Dial.	
Expt. No.	Aq.	Pl.	Aq.—Pl.	Aq.	Pl.	Aq.—Pl.	Aq.	Pl.
1	297.5	296.2	+1.3	304.2	296.8	+7.4	−6.7	−0.6
2	293.9	295.3	−1.4	298.6	299.5	−0.9	−4.7	−4.2
3	293.5	289.8	+3.7	294.4	297.7	−3.3	−0.9	−7.9
4	295.3	300.5	−5.2	299.1	298.6	+0.5	−3.8	+1.9
5	296.0	296.5	−0.5	302.0	292.0	+10.0	−5.0	+4.5
Mean	295.2	295.7	−0.4	299.7	296.9	+2.7	−4.2	−1.3

TABLE 3.—*Potassium Concentrations*

	Potassium Concentrations, mM./Kg. Water							
	Control			Dialysis			Cont.—Dial.	
Expt. No.	Aq.	Pl.	Aq./Pl.	Aq.	Pl.	Aq./Pl.	Aq.	Pl.
1	5.5	6.3	0.875	6.0	6.5	0.923	−0.5	−0.2
2	5.7	6.6	0.864	6.2	6.5	0.954	−0.5	+0.1
3	5.2	5.8	0.897	5.4	5.8	0.931	−0.2	0.0
6	4.1	4.1	1.00	4.0	4.0	1.00	−0.1	+0.1
7	4.6	5.2	0.885	4.7	5.0	0.940	+0.1	+0.2
Mean	5.0	5.6	0.904	5.1	5.6	0.950	−0.4	0.0

The results in Table 3 illustrate that there was no transfer of potassium from aqueous to plasma following dialysis. Unlike sodium, the potassium concentration in the aqueous is not in excess of the membrane equilibrium requirements.

Comment

The results of aqueous-to-plasma dialysis obtained by Duke-Elder et al. supported the concept of aqueous hypertonicity across the barrier by demonstrating a sodium excess in the aqueous. While the results of the present investigation confirm the finding of an excess sodium salt in the aqueous, they demonstrate that this excess is to a large extent osmotically balanced by a deficiency of other substances in the aqueous.

The results of the present investigation do not support Friedenwald's hypothesis of a primary transport of a bicarbonate ion with a secondary transfer of a cation by electrostatic attraction.[3] As the ion mobility of the potassium ion is greater than that of the sodium ion,[2] the secondary transport of a cation should favor the potassium ion, an expectation that is not consonant with the results of the dialysis experiments.

It should be noted that the plasma utilized for dialysis was not obtained from the ocular capillaries, and so any interpretation in terms of the blood-aqueous barrier assumes a uniformity of composition between plasma in the large vessels or heart and in the ocular capillaries.

Summary

The results of aqueous-to-plasma dialysis in the rabbit demonstrate an aqueous excess of sodium, although no aqueous excess of potassium is present. The excess sodium is to a large extent osmotically balanced by aqueous deficiencies of other substances, presumably nonelectrolytes.

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The Effect of Intramuscularly Administered Trypsin on Blood Injected into the Vitreous of Rabbits

MARGARET R. CHANDLER, M.B., B.S. (London), and ERNEST ROSENTHAL, M.D., New Haven, Conn.

Clearing of vitreous hemorrhages is variable and unpredictable in spite of measures used to accelerate absorption (von Sallmann,[1] Lepri[2]). Crystalline trypsin in sesame oil was first studied by Hopen and Campagna (1954)[3,4] in patients with various ocular conditions. Good results were noted, following its intramuscular administration, in 16 cases of extraocular trauma and in 5 patients with postoperative hyphema. In two of five patients with vitreous hemorrhages improvement was attributed to trypsin. One patient showed complete clearing in eight weeks, whereas the hemorrhage of the second was partially clear in four weeks.

The mode of action of trypsin is not certain, but various investigators have stressed the anti-inflammatory and thrombolytic effects.[5,6] Following the report of Hopen and Campagna, intramuscularly administered trypsin has been tried in this hospital in a small series of patients with diabetic vitreous hemorrhages, and the results observed prompted a controlled experiment on rabbits. It is the purpose of this paper to describe the effects of the use of intramuscularly administered trypsin on fresh blood introduced into the vitreous body of 16 rabbits.

Technique of Blood Injection into the Vitreous Body

Both eyes of 16 adult male albino rabbits were used. These animals weighed from 3 to 3.5 kg. and were fed entirely on Purina Rabbit Chow. The injection was carried out with use of general anesthesia, pentobarbital sodium (30 mg. per kilogram of body weight) and ether or pentobarbital and chloroform, when diathermy was applied to the sclera. After exposure of the sclera in the region of the superior rectus muscle, 0.1 ml. of blood was withdrawn from the ear vein of the same animal into a siliconized or heparinized 0.25 ml. syringe. This blood was immediately injected into the center of the vitreous body through a 24-gauge needle which pierced the sclera 5 mm. beyond the limbus and adjacent to the tendon of the superior rectus. The scleral puncture site was treated with diathermy in the six last animals. The conjunctival incision was then closed, and atropine 1% and sulfacetamide 30% were instilled in each instance. The fur was clipped short over both thighs and the skin was cleaned with hexachlorophene (pHisoHex) prior to trypsin injection; dry sterilized needles and syringes were used throughout. The trypsin was provided by the National Drug Company, Philadelphia, as Parenzyme, a preparation of 5 mg. of crystalline trypsin in 1 ml. of sesame oil.

Method of Study

The animals were divided into three groups. Group 1 consisted of six control rabbits who did not receive trypsin. Group 2 comprised three animals whose daily dose of tryspin was 0.5 mg. In Group 3 were six rabbits who were given 2.5 mg. trypsin daily. An additional animal received 7.5 mg. daily. The last four of the animals studied (three in Group 3; Table) were first given trypsin injections four days prior to the

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From the Department of Surgery (Section of Ophthalmology), Grace-New Haven Hospital, Yale University School of Medicine.

Clinical Findings in Control and Trypsin-Treated Rabbits

Trypsin Dose	Start of Injections	Treatment of Blood in Syringe	Animals, No.	Day on Which Sign Was First Noticed: Vitreous Clouding & Dense Red Clot	Clot Fragmentation & "Whitening"	Fibrous Tissue Formation	Detached Appearance of Retina	White Patches on Retina	Peripheral Vitreous Clearing	Central "Spider Web" Clot, Clear Peripheral Vitreous
Group 1 Control		Silicone	3	3	7	8	15	15	21	42
				3	7	10	12	13	30	40
				3	6	9	10	16	30	42
		Heparin	3	3	7	13	--	16	33	39
				2	6	10	--	13	30	39
				3	7	9	11	13	30	42
Group 2 0.5 mg.	At operation	Silicone	2	3	6	8	9	13	27	42
				2	6	7	8	13	30	39
	At operation	Heparin	1	3	7	8	--	10	33	42
Group 3 2.5 mg.	At operation	Silicone	2	4	6	9	13	10	30	39
				3	6	7	8	13	33	42
	At operation	Heparin	1	2	6	7	9	13	33	39
	4 days before operation	Heparin	3	3	6	8	10	13	30	42
				3	5	7	--	16	7	--
				3	6	7	10	16	30	39
7.5 mg.	4 days before operation	Heparin	1	4	5	6	9	10	27	42

introduction of the blood into the vitreous, whereas the injections in the remainder in Groups 2 and 3 commenced on the day of operation. The trypsin was discontinued in all instances after six weeks. Ophthalmoscopy under phenylephrine (Neo-Synephrine) mydriasis was carried out daily for the first week and then every third day for five weeks. At the end of the six-week period of observation the animals were killed and the eyes were prepared for microscopy.

Results

Ophthalmoscopy.—The behavior of the blood mass in the vitreous as observed ophthalmoscopically in all three groups was singularly uniform. On the day following the injection of the blood a central red mass of variable shape, mostly globular, was evident, with only slight diffusion into the vitreous. The fundus was otherwise clear. All eyes showed the same appearance regardless of previous administration of trypsin. Heparinizing or siliconizing the syringe caused no significant difference in appearance.

By the end of the first week the mass showed partial fragmentation and became whitish-gray. The vitreous itself was less transparent by the third day and was definitely clouded by the seventh day. Between the 7th and 13 days white fibrous-tissue-like strands made their appearance within and around the blood mass, radiating in particular toward the site of the scleral puncture. In most instances the mass became almost encapsulated by this tissue, which, in addition, fanned outward to superimpose itself upon the retina, giving the appearance of a detachment. Whitish patches on the retina became visible at the end of the second week. After the end of the third and fourth weeks the peripheral vitreous haze began to clear, and this clearing was complete by the end of the sixth week. The final appearances were almost identical. The blood mass assumed the appearance of a fine white "spider web" in the center of the vitreous and behind the posterior lens pole (Fig. 1). Attached to the "web" were whitish fibers radiating toward the scleral perforation and, to a lesser extent, to the opposite side of the retina. The vitreous immediately adjacent to the former blood mass showed aggregates of punctate opacities, while at the periphery it was transparent. In only one eye did the peripheral vitreous fail to clear. In every instance white dense patches were scattered across

Fig. 1.—Appearance of the vitreous after six weeks.

the retina. The time sequence of the ophthalmoscopic findings in the three groups is summarized in the Table.

Microscopic Studies.—After fixation of the eyes in formalin, sections were cut through the blood mass and adjoining vitreous and retina. All sections were stained with hematoxylin and eosin, and a few were stained with Turnbull's blue. Characteristic changes were noted in the blood mass, adjacent vitreous, and retina.

Appearance of Former Blood Mass.—In all sections examined the blood mass showed close aggregates of lysed red cells in various stages of disintegration. In addition, occasional single nucleated round cells and larger numbers of macrophages were visible. The latter were filled with granules giving a positive iron stain and appeared both within the blood mass and in the amorphous surrounding vitreous. Variable fibroblastic reactions, usually in the periphery of the blood mass, occurred in five eyes. Three of these came from animals in Group 3; One, from the control group, and a particularly intense fibroblastic reaction affected the blood mass of one eye in the animal receiving 7.5 mg. of trypsin daily (Fig. 2). The surrounding vitreous presented no significant changes in either group and appeared to be devoid of cells.

Appearance of Adjacent Retina.—The retinal changes were confined to Müller's fibers in the interstices of the nerve fiber layer and the inner limiting membrane. In most instances the fibers of Müller became thickened in the interstices and along the inner limiting membrane, already some distance from the actual blood mass. Nearer the blood mass the inner limiting membrane gave a duplicated appearance, and im-

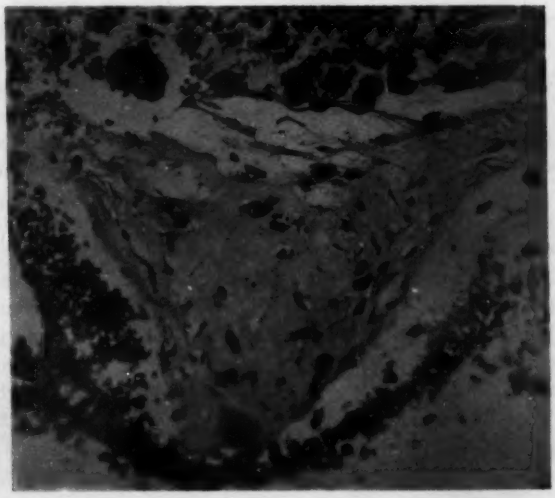

Fig. 2.—Left eye of rabbit treated with 7.5 mg. of trypsin daily, showing fibrous tissue in blood mass.

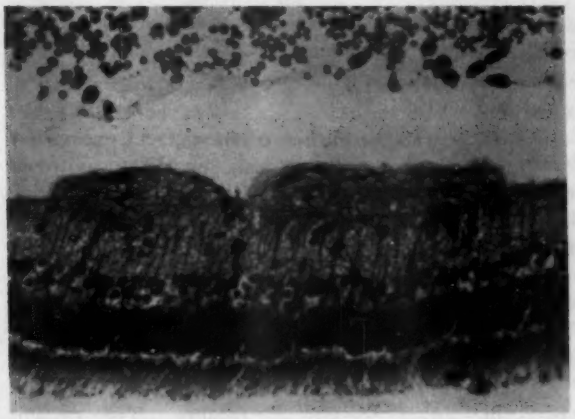

Fig. 3.—Proliferation of the internal limiting membrane near blood mass; × 325.

mediately beneath the mass a network of glial fibers was formed (Fig. 3). This network, coming from the thickened inner limiting membrane, extended into the vitreous and surrounded iron-laden macrophages. Elsewhere large clumps of macrophages settled on the inner limiting membrane and broke off into the vitreous. Other retinal layers showed no obvious abnormalities. This pattern of retinal change applied to a variable extent to all the eyes examined except for one animal in Group 3 and one eye of the animal receiving 7.5 mg. of trypsin daily (Fig. 4). Pröbsting (1892) [7] and Oguchi (1913) [8] observed a somewhat similar behavior of blood injected into rabbit vitreous both ophthalmoscopically and histologically. The former author reported that retinal detachment was a constant finding. This did not occur in the present experiments, even when scleral diathermy was not used.

Comment

The observations of Hopen and Campagna (1954) suggested that there might be a direct relationship between the clearing of extravasated blood in or near the eye and the administration of trypsin. It was also thought that any possible acceleration of blood absorption with previous clot organization could be attributed to the use of the enzyme, in view of the known activation of trypsin on the intrinsic plasma fibrinolytic system.[9] While it would be reasonable to expect a direct action of trypsin on extrav-

Fig. 4.—Right eye of rabbit treated with 7.5 mg. of trypsin daily, showing normal retina in contact with blood mass; × 325.

asated blood in ecchymoses around the eye, where a capillary bed abounds, the conditions within the vitreous are not analogous. According to Fuchs (1919),[10] blood in the vitreous behaves in different ways. It may stay fluid for a long time because of an absence of substances in the vitreous which cause the disintegration of platelets. Occasionally erythrocytes swell, but they may also remain unchanged for years. Fibrin formation, according to Fuchs, follows inflammations associated with large vitreous hemorrhages, and as such it is rare in most medical disorders associated with vitreous bleeding. Therefore, in the absence of fibrin formation, in the early phase of a vitreous hemorrhage, trypsin would be unlikely to exert a useful therapeutic action. The reabsorption of blood from the vitreous, in the absence of clot formation, sometimes appears to be very slow compared with that from ecchymoses. This is probably related to the distance of normally acting capillaries from the center of the vitreous, and it is also doubtful if trypsin has any action on the retinal capillaries and their capacity to reabsorb blood.

In studies with intramuscularly given penicillin, Leopold[11] found that in doses of 4000 units per kilogram the vitreous failed to show detectable concentrations, while Sorsby,[12] using 1,000,000 units, noted only low levels, which fell in less than 15 hours. While we are not aware of similar studies in respect of trypsin estimations in the vitreous, the possibility of the enzyme failing to reach the site of hemorrhage needs to be considered, and it is of interest that the studies of Sherry et al.[13] showed that after the intravenous infusion of trypsin in dogs only a very small percentage could be detected in the blood. In the present studies no significant action of trypsin could be found on the behavior of blood injected into the vitreous of rabbit eyes observed for 42 days, over that of the control animals, and the histological findings in both the control and the treated groups, regardless of dosages administered, were almost identical. Similar histological observations were reported in respect to the use of streptokinase and streptodornase by Dorello and Ronchieri (1954).[14]

The conditions of the present experiment do not compare with spontaneous vitreous bleeding of certain disorders in man, owing to the failure of diffusion of the injected blood throughout the rabbit vitreous. Boruchoff and Woodin (1956)[15] drew attention to a species difference in vitreous composition, and it may well be true that such a difference obtains in respect to human and rabbit vitreous composition which could affect trypsin diffusibility. The present experiment also has, apparently, failed to establish a minimum effective dose for trypsin to be therapeutically active in rabbit vitreous, as the high dosage of 7.5 mg. in one animal did not influence the slow clearing of the blood clot or prevent a fairly extensive fibroblastic reaction. This dose was nevertheless in excess, weight for weight, of the dosages used by Hopen and Campagna (1954) for which certain therapeutic deductions were made.

Summary

The effect of trypsin on the clearing of experimentally induced vitreous hemorrhages was studied in rabbits. Variable doses were administered to 10 rabbits, and 6 animals served as controls. Continuous ophthalmoscopic observations over 42 days in the treated and control series have been recorded as well as the final histology of the injected blood and retina. While significant differences in the blood clot behavior or its histological appearances could not be discerned between the trypsin-treated and control animals, the conditions of the experiment precluded definite therapeutic deductions.

Dr. David Freeman interpreted the pathological findings; Dr. I. H. Leopold gave advice about preparation of the blood, and Drs. P. K. Bondy and R. M. Fasanella gave advice and encouragement.

Yale University School of Medicine, 789 Howard Ave. (4).

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The Viscosity of the Vitreous Humor Influenced by Hormones

GODFRED LARSEN, M.D., New York

During the last few years several papers on the structure and chemistry of the vitreous body have appeared, but many problems remain unsolved. At the present time the vitreous humor is mostly considered to be a transparent acellular avascular gel, consisting of a fibrous solid material and a viscous solution. The former, known as the residual protein, has many features in common with collagen (Pirie et al., 1948 [1]; Matoltsy, 1952 [2]). The viscous fluid obtained after removal of the residual protein is known to contain one acid mucopolysaccharide, hyaluronic acid, as well as soluble proteins. The hyaluronic acid, first found by Meyer and Palmer (1934, 1936) [3,4] in bovine vitreous, is an important part of a large group of natural polyelectrolytes. The hyaluronic acid is present in the fine network of fibrils of the vitreous, which is reinforced by the hydrated hyaluronic-acid molecules (Balazs, 1954 [5]); it lends the filtrate its consistency and viscosity, a viscosity which is much lower than, e. g., that of the synovial fluid (Kulonen, 1951 [6]). The viscosity of the soluble filtrate and the content of hyaluronic acid vary in different species of animals (Meyer et al., 1938 [7]). The viscosity of the ocular fluids has been investigated previously by Cavazzani (1905 [8]) and by Scalinci (1907 [9]). They found the viscosity of the vitreous to be much higher than that of the aqueous humor. Cohen, Killian, and Kamner (1928 [10]) noted a considerable variation in the viscosity of bovine vitreous, ranging from 16.62 to 21.50×10^{-3} in C. G. S. units at 20 C. Friedenwald and Stiehler (1935 [11]) made the first comprehensive examination of the viscosity in the vitreous body of beef. Woodin and Boruchoff (1955 [12]) also determined the viscosity of beef vitreous, and recently the same authors (1956 [13]) have published a work on the viscosity and the hyaluronic acid content of vitreous from rabbits, finding the viscosity of the filtrate much lower than that of the beef vitreous and not depending on shear rate.

As the ground substance of connective tissue is known to be influenced by hormones provoking chemical changes reflected in changes in the stainability and permeability of the ground substance (Opsahl, 1949 [14]; Shumann and Finestone, 1950 [15]; Asboe-Hansen, 1950 [16]; Videbaek et al., 1950 [17]; Asboe-Hansen, 1952 [18]; Cavallero and Braccini, 1951, [19] and others) it is reasonable to believe that the hyaluronic acid of the vitreous might be influenced as well. Hormones with direct effects on the mucopolysaccharides are the corticotropic hormone, the adrenocortical steroids cortisone and hydrocortisone, the thyrotropic hormone, and the thyroid hormone. The first group is known to cause a reduction of the metachromatic material of the ground substance (Asboe-Hansen, 1950 [16] and 1952 [18]). The thyrotropic hormone is found to increase the amount of mucopolysaccharides in connective tissue (Asboe-Hansen and Iversen, 1951 [20]), whereas the thyroid hormone counteracts this effect (Asboe-Hansen, 1950 [21]).

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Connective Tissue Research Laboratory, University Institute of Medical Anatomy, Copenhagen. Present address: Ophthalmology Research, Columbia University College of Physicians and Surgeons.

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Material and Methods

Throughout the experiments 244 rabbits were used, 18 of which were females. The weight of the animals varied from 2000 to 3000 gm. Of these rabbits, 49 were used as controls.

In one group of rabbits vitreous filtrate was taken from 10 animals and treated in vitro with 50 V. R. U. of testicular hyaluronidase * in 0.1 ml. of isotonic saline during six hours. These were compared with 10 other samples of vitreous filtrate after addition of the same amount of isotonic saline.

One group of 32 rabbits was injected with cortisone acetate, 25 to 50 mg. daily, for 10 to 14 days.

Thirty rabbits were thyroidectomized. The same number of rabbits were thyroidectomized and, about two weeks later, treated with thyrotropic hormone,† 8 to 12 U. S. P. units daily during 10 days. The thyroidectomy was checked by measuring the uptake of radioactive iodine (I^{131}) in the thyroid area, and the radioactivity there was compared with the activity of indifferent places of the body of the rabbit. Only rabbits which showed values of radioactivity of the thyroid area on the same level or less than those of the indifferent places were used.

In the last group 27 rabbits were treated daily for seven days with 0.5 mg. of thyroxin. The effect was checked by several weighings of the animals; all of them were losing considerable weight.

The intraocular pressure was measured with a Schiøtz tonometer; the 7.5 gm. weight was used for all the experiments. The tonometer was specially calibrated for eyes of living rabbits, the pressure being about the same as in man. The tension was determined with the animals anesthetized with ether; care was taken to keep them in the same depth of anesthesia all the time. Several determinations were done on each animal.

The viscosity was measured in a special viscosimeter of Ostwald's type, consisting of a capillary tube 0.29 mm. in diameter; the minimum volume necessary for measuring the viscosity was 0.4 ml. The viscosimeter was kept in a thermostat at a constant temperature of 30 C. The vitreous humor was removed from freshly enucleated eyes, and the relative viscosity was measured shortly after. Distilled water was used as a control. After each determination the viscosimeter was carefully cleaned and dried. The viscosity of distilled water was checked repeatedly.

The vitreous body was carefully dissected free from the ocular tissues and poured into a sterilized glass. One drop of 0.5% diethyldithiocarbamate and toluene was added to prevent a possible depolymerization by copper ions and ascorbic acid or any other decomposition. After homogenization the vitreous fluid was passed through a glass filter with pores of about 5μ.

The eyes of the first experimental rabbits were enucleated simultaneously, but the viscosity was found to be very low, and rather considerable individual variations in the viscosity occurred. Therefore, in the following experiments one eye of a rabbit was first removed and the viscosity was measured; two to three weeks later the other eye was enucleated, and the viscosity of that eye was compared with that of the first one. All the animals in the various groups were thereafter treated in this way.

Results

The viscosity was found to be very stable, with only small changes in the viscosity of the filtrate, when it was left either in the refrigerator or at room temperature for several days.

Table 1 shows that very small differences were observed between the viscosities of the vitreous bodies from the same normal rabbit, the average viscosity being nearly the same. The viscosities of vitreous bodies from a pair of eyes enucleated simultaneously did not differ from those of eyes removed sepa-

* Hyalas Leo, produced in Hälsingborg, Sweden.

† The thyrotropic hormone was supplied by Parke, Davis & Company, Detroit.

TABLE 1.—*The Relative Viscosity of Vitreous from Normal Rabbits*

Group	Cases, No.	Relative Viscosity *		
		Range	M ± ε (M)	σ
Left eyes	49	1.113–1.196	1.144±0.002	0.016
Right eyes	49	1.100–1.204	1.145±0.003	0.018

* Differences between left and right eyes with regard to average viscosity are as follows: D=0.00086; t=0.91; P=0.4. Abbreviations are as follows: M=arithmetic mean; ε (M)=standard error of mean; σ=standard deviation; D=difference; t=t according to "Student"; P=significance level.

rately. No differences, except individual variations, occurred in the viscosities of vitreous bodies from 10 female rabbits.

Table 2 shows that the viscosity is dependent on the content of hyaluronic acid.

TABLE 3.—*The Relative Viscosity of Vitreous from Rabbits Treated with Cortisone*

Group	Cases, No.	Relative Viscosity *		
		Range	M ± ε (M)	σ
Left eyes	32	1.119–1.178	1.142±0.002	0.011
Right eyes	32	1.128–1.209	1.167±0.003	0.015

* Differences between left and right eyes with regard to average viscosity are as follows: D=0.025; t=12.42; P<0.001.

After treatment with hyaluronidase the viscosity dropped to the level of distilled water, whereas addition of the same amount of isotonic saline resulted in only a very little decrease. It is easily seen also that the contribution of the proteins to the total viscosity of the vitreous filtrate is very small.

TABLE 5.—*The Relative Viscosity of Vitreous from Thyroidectomized Rabbits Treated with Thyrotropic Hormone*

Group	Cases, No.	Relative Viscosity *		
		Range	M ± ε (M)	σ
Left eyes	32	1.122–1.181	1.144±0.003	0.016
Right eyes	32	1.163–1.243	1.190±0.004	0.020

* Differences between left and right eyes with regard to average viscosity are as follows: D=0.047; t=23.38; P<0.001.

In the cortisone-treated group of animals, it is evident from Table 3 that the treatment increased the viscosity significantly; the average increase was about 2.2%. Two animals did not respond.

The thyroidectomized rabbits (Table 4) also showed a rise in the viscosity, this being, however, not of a similar degree, but still significant.

TABLE 2.—*The Relative Viscosity of Vitreous Before and After Treatment with Hyaluronidase and with Saline in Vitro*

Group	Cases, No.	Relative Viscosity		
		Range	M ± ε (M)	σ
Untreated	10	1.127–1.178	1.146±0.004	0.013
Treated with hyaluronidase	10	1.032–1.048	1.039±0.001	0.004
Untreated	10	1.128–1.161	1.143±0.003	0.009
Treated with saline	10	1.125–1.157	1.140±0.003	0.009

Treatment with thyrotropin in the thyroidectomized rabbits (Table 5) resulted in a considerable rise in the viscosity, greater than in any other group; the average increase was about 4.0%.

TABLE 4.—*The Relative Viscosity of Vitreous from Thyroidectomized Rabbits*

Group	Cases, No.	Relative Viscosity *		
		Range	M ± ε (M)	σ
Left eyes	30	1.129–1.171	1.145±0.002	0.011
Right eyes	30	1.135–1.171	1.150±0.002	0.009

* Differences between left and right eyes with regard to average viscosity are as follows: D=0.0058; t=3.89; P=0.001.

The viscosity of vitreous filtrate from thyroxin-treated animals (Table 6) remained almost unchanged. A slight decrease was not found to be significant.

The intraocular pressure showed no change in any experiment (Table 7). Relatively wide variations, ranging from 18 to

TABLE 6.—*The Relative Viscosity of Vitreous from Rabbits Treated with Thyroxin*

Group	Cases, No.	Relative Viscosity *		
		Range	M ± ε (M)	σ
Left eyes	27	1.127–1.166	1.145±0.002	0.010
Right eyes	27	1.131–1.169	1.144±0.002	0.011

* Differences between left and right eyes with regard to average viscosity are as follows: D=0.0009; t=0.9; P=0.35.

TABLE 7.—*The Intraocular Pressure Measured with a Schiøtz Tonometer*

Group	Av. Intraocular Pressure, Mm. Hg	
	Left Eyes (Control)	Right Eyes
Normal	22.3	23.7
Cortisone	24.1	22.8
Thyroidectomy	23.2	21.8
Thyroidectomy + thyrotropin	23.7	24.4
Thyroxin	22.7	23.4

28 mm. Hg, were found in the same animal at different times.

Comment

The physicochemical properties of hyaluronic acid are, no doubt, of importance to the stability of the vitreous gel. Consisting of glucuronic acid-N-acetylglucosamine units, hyaluronic acid is supposed to have an unbranched chain (Meyer, 1936 [4] and 1947,[22] and others), the length of the chain averaging 4800 A. (Blix and Snellmann, 1945 [23]) or 7000 to 10,000 A. (Brunish et al., 1954 [24]) in beef vitreous as shown by flow birefringence. Light-scattering measurements have given information about the molecular weight. The values of Laurent (1955 [25]) varied from 350,000 to 500,000, those of Brunish et al. (1954 [24]) from 500,000 to 1,000,000. Hyaluronic acid contains hydroxyl and carboxyl groups with repeating 10 A. intervals, yielding a high viscosity even in low concentrations.

The changes in viscosity of the vitreous filtrate found here indicate that some variations of hyaluronic acid in the vitreous may take place.

The rise in the viscosity elicited by treatment with cortisone was not expected, but very little is known about the effect of cortisone on mucopolysaccharides. Histochemistry has shown that the metachromasia of the ground substance in connective tissue is reduced following treatment with cortisone. Kulonen (1951 [6]) found an increase of viscosity and glucosamine content of synovial fluid, and Smelser and Ozanics, (1955 [26]) an augmentation of exophthalmos induced by cortisone in guinea pigs treated with pituitary extracts, indicating an increase of the water-binding capacity of the mucopolysaccharides.

Thyroidectomy caused a slight increase of viscosity. Removal of the thyroid is known to entail an accumulation of mucopolysaccharides in skin and joints, presumably through a preponderance of thyrotropic hormone, which in a thyroidectomized organism is not counteracted by thyroid hormone.

In the thyroidectomized group treated with thyrotropin a considerable rise was found. Thyrotropic hormone also provokes an accumulation of acid mucopolysaccharides in other connective tissues, as shown in exophthalmos experiments. The stimulus may not be qualitatively different from that of thyroidectomized organisms, the difference being only a question of quantity. Thyrotropic hormone acts directly on the hyaluronic acid of the vitreous or the synthesis of it, because no thyroid gland was present in these experiments.

There was no significant effect of thyroxin on the last group of animals, in spite of the fact that thyroid hormone is known to decrease the amount of acid mucopolysaccharides in connective tissues.

The changes of viscosity mentioned above were not reflected in variations in the intraocular tension of the eyes, perhaps because the changes were too minimal or because the eye may be able to compensate and regulate the production and the outflow of its fluids.

The factors responsible for the variations of the viscosity may be changes in the concentrations of the hyaluronic acid or in the degree of polymerization of this mucopolysaccharide or a combination of these factors. In fact, varying concentrations have been found by me (to be published). Other possible factors of importance to the viscosity might be the interactions or bindings of hyaluronic acid to the proteins. Jensen et al. (1955 [27]) found that the nonfibrous proteins act together with the hyaluronic acid in stabilizing the vitreous gel. Whether or not the hyaluronic acid is bound to the proteins is not known for certain. The investigations of Blix (1940 [28]) showed that the hyaluronic acid is not combined with the proteins of the vitreous.

A relationship between the variations of the hyaluronic acid in the eye and glaucoma has been suggested by many authors (Meyer, 1947 [22]; Brunish et al., 1954 [24]; Schweer, 1956 [29]). The present investigation did not support this idea.

Summary

Cortisone, thyroidectomy, and thyroidectomy plus thyrotropin increased the viscosity of the vitreous filtrate of rabbits. The response to cortisone was in between the responses to the two other treatments. The viscosity remained unchanged under treatment with thyroxin.

The intraocular presure, determined with a Schiøtz tonometer, was not affected.

The factors responsible for the changes of the viscosity are discussed.

630 W. 168th St. (32).

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Epibulbar Nevoxanthoendothelioma

DAVID G. COGAN, M.D.; TOICHIRO KUWABARA, M.D., and DAVID PARKE, M.D., Boston

Nevoxanthoendothelioma is a dermatologic and pathologic syndrome occurring almost exclusively in infants or children and characterized by histiocytic tumors in the skin and, occasionally, elsewhere. The name is somewhat of a misnomer, since the lesions are not necessarily congenital nor are they proved to be derived from endothelial cells, but the name has served successfully to distinguish the entity from other xanthomas and is now widely accepted.

The individual lesions of nevoxanthoendotheliomas resemble those of the Christian-Schüller syndrome. Unlike this latter, however, nevoxanthoendothelioma is relatively benign and resolves spontaneously in a matter of months or years. Its etiology is totally obscure, and no treatment has been found that hastens the resolution of the lesions.

Ocular manifestations of nevoxanthoendothelioma were first studied by Fry (1949) in a case reported by Blank et al.[1] Subsequently, about nine instances of eye lesions with nevoxanthoendothelioma have been observed and are to be reviewed in the near future by Sanders.[2] All of these cases have been characterized by granulomatous infiltration of the iris.* The patients have all been infants, and the presenting symptom in most of the cases has been "spontaneous" hemorrhage into the anterior chambers. To our knowledge, an epibulbar xanthoma has not heretofore been recognized as the presenting symptom of nevoxanthoendothelioma. It is the purpose of this report to describe such a case.

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Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

* The iris lesions of nevoxanthoendothelioma are not to be confused with the secondary deposition of lipid in the iris, which has also been called xanthomatosis.[3-5]

Report of a Case

The patient was a 5-year-old girl whose chief complaint was photophobia and blepharospasm of one and one-half years' duration. The onset had been insidious and had not been known to be associated with trauma or other significant abnormality.

Examination within a few weeks of the onset showed several small yellowish masses at the limbus of either eye. These were likened to phlyctenules. According to the parents these lesions had not been present previously. The patient was given cortisone topically, but the lesions increased slowly in size.

Examination four months after the onset showed a somewhat elevated yellowish mass measuring about 4 mm. in diameter situated at the limbus in the 11 to 1 o'clock position of the right eye (Fig. 1) and a similar lesion at the 6 to 9 o'clock position in the left eye (Fig. 2). In addition, there was a smaller but otherwise similar lesion in the 12 o'clock position of the left eye. All the lesions were fed by several sizable vessels from the conjunctiva and were heavily vascularized. The two larger lesions extended several millimeters into the cornea and appeared to involve most of the thickness of the stroma. They were yellow and were nonfluorescent. The irides, media, and fundi were normal.

The patient also had several small erythematous papules on her lids and numerous papules in each axilla (Fig. 3). Except for these she was entirely normal. She was a well-developed and active girl, with no suggestion of splenomegaly or hepatomegaly. There was no history of diabetes insipidus or of recurrent abdominal

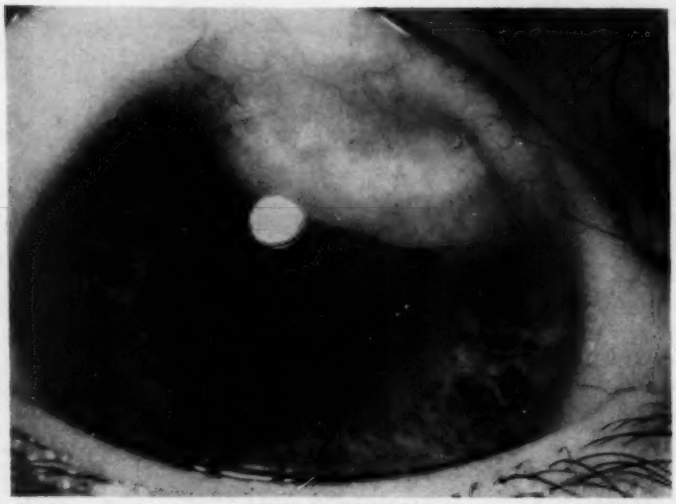

Fig. 1.—Right eye, showing tumor mass in upper portion of limbus. This involved all layers of the cornea.

pain. X-rays of the chest and skull were normal. The blood cholesterol was 158 mg. per 100 cc., and cholesterol ester, 117 mg. per 100 cc. The N. P. N. was 27 mg. per 100 cc. The urine was normal, with a specific gravity of 1.020.

The three lesions were partially excised. This resulted in considerable subjective improvement, but eight months after the excision the lesion in the right eye again increased somewhat in size. The lid lesions had disappeared, but there continued to be small red papules in both axillae. These latter were again biopsied.

Histologic examination of the ocular lesions gave the following information.

The tumors consisted of masses of cells consisting for the most part of foam cells, with interspersed lymphocytes, connective tissue, and blood vessels (Figs. 4A and 4B). A few small giant cells were present on the periphery of the lesions, but there were no Touton giant cells. On one side of the tumor the cells bordered abruptly on normal cor-

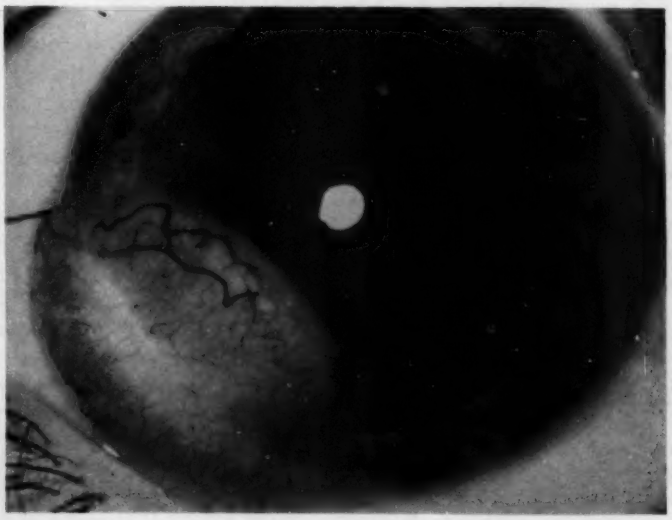

Fig. 2.—Left eye, showing tumor mass bridging the limbus in lower nasal quadrant. This also involved all layers of the cornea.

Fig. 3.—Axilla, showing numerous papules. These were yellow and were slightly elevated. They were not accompanied by any evident erythema.

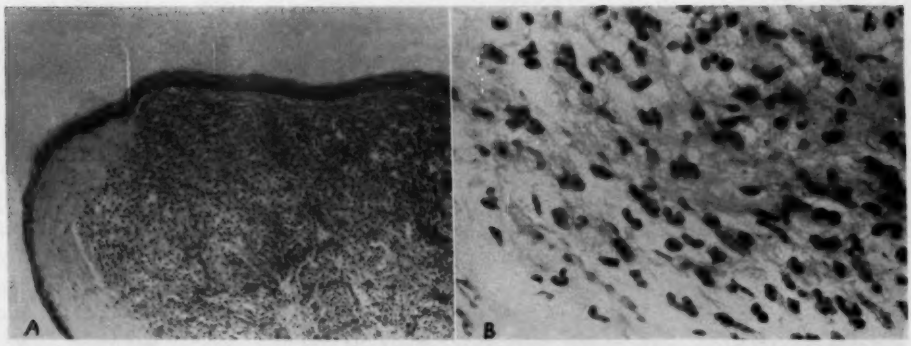

Fig. 4A.—Tumor of limbus. The left portion of the field shows normal corneal stroma. The tumor mass abuts against this stroma abruptly. Hematoxylin and eosin; reduced about 40% from mag. × 6.3.

Fig. 4B.—Same section showing predominantly histiocytes and lymphocytes; reduced about 40% from mag. × 40.

neal stroma, and on the other side the tumor merged into conjunctival tissue which was slightly infiltrated with round cells. The overlying epithelium was entirely normal. There was no necrosis.

Sections cut in the frozen state and stained with Sudan showed an abundance of sudanophilic globules and birefringent crystals in selective portions of the tumors. It was noteworthy that the fat-containing portions were not clearly distinguishable from the fat-free portions in the routine sections that had been embedded in paraffin and stained with hematoxylin and eosin. Both areas contained predominantly histiocytes, but the Sudan preparations showed the stainable fat to be found only in a portion of the tumors, estimated to be less than 50%.

The sudanophilic material consisted for the most part of brilliantly red globules of various sizes within the cells. The fat-containing cells were chiefly the histiocytes, but some fat was present in spindle cells, thought to be fibrocytes, and even in some of the bordering cells of the corneal stroma and of

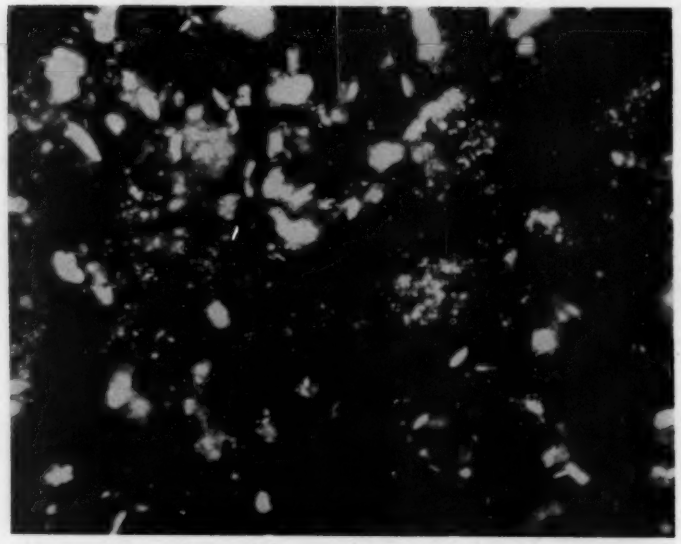

Fig. 5.—Photograph taken with use of crossed Polaroids of section cut in the frozen state and unstained. Noteworthy are the rod-shaped crystals and the spherocrystals (Maltese crosses).

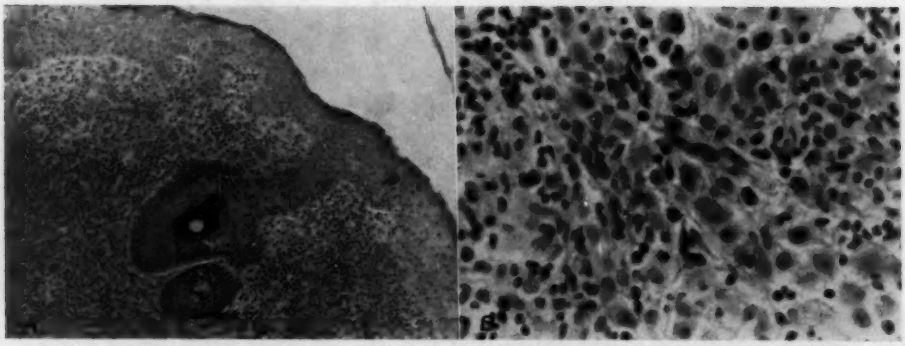

Fig. 6A.—Axillary tumor. The cells consisted predominantly of histiocytes and lymphocytes. The overlying epithelium was normal. Hematoxylin and eosin; reduced about 40% from mag. × 10.

Fig. 6B.—Same section showing details of cell types; reduced about 40% from mag. × 40.

the epithelium. No sudanophilic material was recognized outside of the cells.

Crystals were abundantly present throughout the same general area as that of the sudanophilic fat. Nevertheless, the crystals were not associated with the globules of fat at the cellular level. In fact, most of the crystals appeared to be extracellular. They were easily recognized with the light microscope as yellowish rods occurring separately or in clusters. With crossed Polaroids they stood out vividly, and most of them were nonsudanophilic. Unstained sections that had been fixed in formalin, cut in the frozen state, and examined with crossed Polaroids showed, in addition to the rod-shaped crystals, masses of tiny spherocrystals that produced Maltese crosses (Fig. 5). These spherocrystals disappeared during the process of Sudan staining, and so their localization in the tissues was not clearly evident, but they appeared to correspond to the globular fat in the foam cells. In contrast to the spherocrystals, the rod-shaped crystals withstood the process of Sudan staining. They were, however, completely removed

by the organic solvents used in the preparation for paraffin embedding.

One of the skin lesions removed from the axilla also showed a tumor made up predominantly of histiocytes with some interspersed round cells and a few polymorphonuclear cells (Figs. 6A and 6B). With paraffin-embedded tissue the histiocytes were seen to be large cells containing a nucleus having one or occasionally several nucleoli. The cytoplasm was homogeneous, and the hyaline, similar to that seen often in giant cells; it was definitely not foamy. The amount of cytoplasm was variable, but often it was abundant. With sections cut in the frozen state and stained with Sudan, no fat globules or crystals were to be found.

Comment

The skin lesions of nevoxanthoendothelioma are clinically similar to the xanthomata of the Christian-Schüller syndrome, and we have seen epibulbar xanthomas with the latter disease that were clinically indistinguishable from those of the present case. Nevertheless, the absence of associated symptoms in the present patient and the patient's general good health would make the Christian-Schüller syndrome most unlikely. The skin lesions were examined microscopically by Dr. Walter Lever, who thought that the heterogeneity of the histiocytes also favored the diagnosis of nevoxanthoendothelioma as opposed to the Christian-Schüller type of xanthoma.

The normocholesteremic values would rule out the juvenile xanthomas that produce tuberous lesions in the skin and tendons. The age of the patient, the exclusively intracellular localization of the lipid, and the limbal site of the lesions would rule out the lipid keratopathy sometimes called xanthomatosis of the cornea.[6]

One of the most intriguing, although not unique, aspects of the lesions was the fact that only a portion of the tumor contained fat and lipoid crystals. This is generally interpreted as representing different stages in the development of the histiocytoma. Also interesting were the two types of birefringence, that of the rod-shaped crystals and that of the spherocrystals. Although we made no study of these, except to note that the latter were more readily soluble in propanol, we have followed the general assumption that the rod crystals were cholesterol while the spherocrystals were cholesterol esters. The sudanophilic globules were presumably neutral fat.

Summary

Epibulbar tumors are described in one patient as the presenting sign in nevoxanthoendothelioma.

243 Charles St. (14).

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Prolonged Survival of the Isolated Retina Induced by Drugs

Strychnine, Mescaline, d-Lysergic Acid Diethylamide (LSD), and Atropine

JULIA T. APTER, M.D., Chicago

Spontaneous and evoked potentials disappear from the electroretinogram (ERG) within four minutes after enucleation of the eyes of experimental animals (Granit).[13] An extinguished ERG is also encountered clinically in senile macular degeneration, occlusion of the central retinal vein or artery, and detachment of the retina.[8,11,18-21,27,28,31] The common factor in these experimental and clinical observations is the dependence of retinal function on an adequate blood supply. Nevertheless, recent reports suggest that the hallucinogenic drugs, mescaline and lysergic acid diethylamide (LSD), potentiate retinal activity despite a reduced blood supply to the retina.

Zádor[34] reported that mescaline restored perception of movement in the blind eye of one of his patients with vascular disease. Klüver[22] presented evidence that mescaline prolongs the ability of the retina to respond to subliminal stimuli from vascular entoptic phenomena. A single clinical test made in my own laboratory demonstrated that the hallucinogen LSD could improve central visual acuity in a patient with senile macular degeneration (Fig. 1).

What is more, previously published studies from this laboratory support these clinical findings that LSD and mescaline may improve the function of an embarrassed retina. The studies[5,6] showed that these

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Northwestern University School of Medicine, Department of Ophthalmology.

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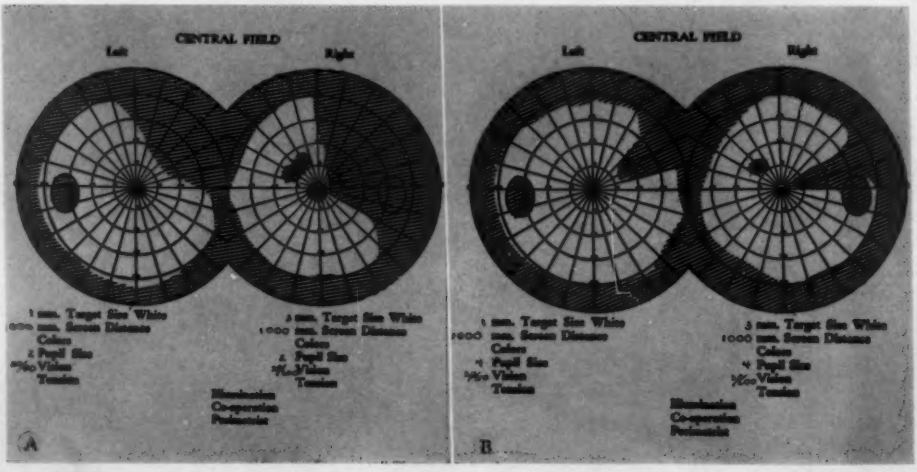
Fig. 1.—Central visual fields of patient, a 64-year-old white man with senile macular degeneration. *A* shows fields present for two years until before administration of 0.05 mg. of LSD. *B* shows fields and improved central visual acuity one and one-half hours after oral administration of LSD.



hallucinogens induce spontaneous potentials in the resting electroretinogram of cats even though the illumination on the retina remained constant. Moreover, spontaneous potentials emanated for four minutes after excision of the eye but photically evoked ERG tracings were elicited for a longer time. This suggested, therefore, that these drugs may prolong the survival time of a retina deprived of its blood supply. Further confirmation of this hypothesis would indicate that such drugs might prove useful in those clinical conditions where the blood supply to the retina is reduced.

The present study was designed to investigate the ability of certain drugs to alter the survival time of the retinas of the excised eyes of cats. One group of drugs was chosen because they all evoked spontaneous potentials and increased the amplitude of the evoked ERG on the intact eye of experimental animals. This group includes strychnine,[32] LSD, mescaline,[5,6] and atropine.[23,32] Since the drugs in this group have side-actions as central nervous system or circulatory stimulants, another group of drugs was selected to test the role these side-actions might play in any positive results obtained. In the second group were epinephrine and ephedrine (circulatory stimulants) and pentylenetetrazol (Metrazol) (central nervous system and respiratory stimulant). The drugs in the second group have no detectable effect on the ERG.

The results of this study indicate that strychnine, mescaline, LSD, and atropine significantly prolong the time the retina of an excised eye shows an evoked ERG if these drugs are given to a cat before enucleation. Pentylenetetrazol, ephedrine, and epinephrine have no effect on the survival of the retina.

Method

Ninety-seven cats were used in these experiments.

In each of 64 cats one eye was removed to determine the length of time this eye was capable of showing photically evoked electrical activity. Half of these cats were given pentobarbital (Nembutal), and half were given curare. The cats given curare had electrodes and tracheal catheter placed with use of local anesthesia with procaine (Novocain). Two insulated platinum wire electrodes were sutured with 000000 nonabsorbable surgical (silk) sutures to the sclera of each eye of each cat immediately after the cats were immobilized in the Horsley-Clarke instrument. One electrode was 9 mm. behind the limbus, and the other was 15 mm. behind the limbus, both being on the same ocular meridian midway between the superior and lateral recti muscles.

These electrodes were led to two channels of a condenser-coupled A. C. amplifier of a Grass electroencephalograph. The time of photic stimulation was recorded by a photo cell placed at the cat's nose. Basal illumination at the cat's eyes was 10 ft-c. The light flash was 100 ft-c. for one-tenth second. One eye was enucleated, and the light flash was presented through the cornea at 15-second intervals until the action potential (ERG) no longer appeared.

Immediately after the first eye was removed, a test drug was administered. The drugs, doses, and routes of administration were as follows: strychnine, 0.1 mg. i. p.; LSD-25, 0.05 mg. i. p. or 0.01 mg. i. v.; mescaline, 10 mg. i. p.; pentylenetetrazol, 10 mg. i. p.; ephedrine, 10 mg. i. p. or 1.0 mg. i. v.; 1:1000 epinephrine, 0.2 cc. i. v.; atropine, 1% solution, 2 drops in conjunctival sac. Strychnine, LSD-25, and mescaline each were used on 14 cats; pentylenetetrazol, on 7; ephedrine, on 5; epinephrine, on 5, and atropine, on 5.

If the test drug was administered intraperitoneally, the second eye was removed 20 minutes later. (I found that spontaneous potentials induced by LSD and mescaline appeared consistently 10 minutes after intraperitoneal administration.) If the test drug was administered intravenously, the second eye was removed 12 minutes later. In the case of atropine, eyes were removed one hour after local instillation. The dura-

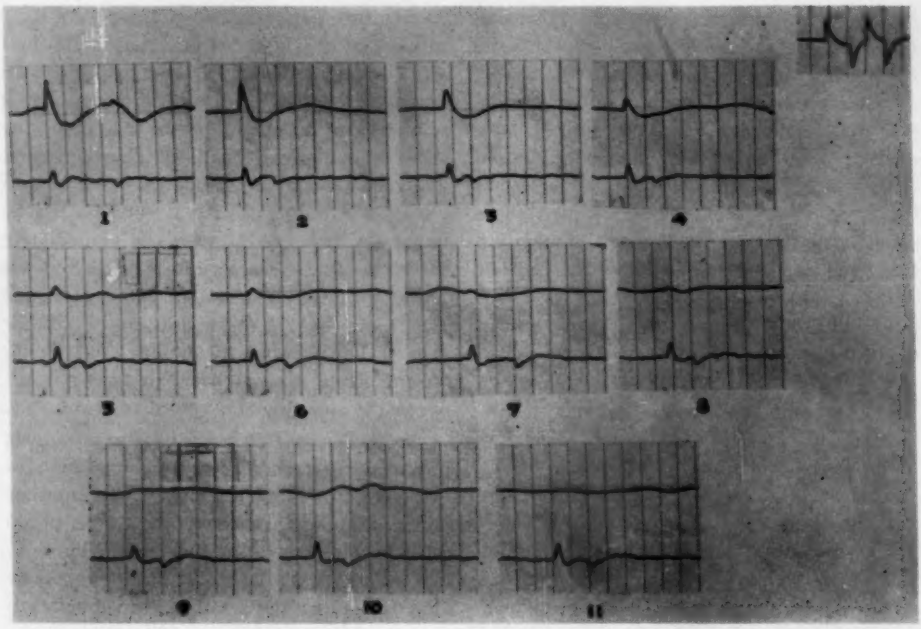


Fig. 2.—Upper tracing from enucleated right eye; lower tracing from intact left eye of a cat to which 42 mg. of pentobarbital per kilogram was administered 90 minutes previously. Light (100 ft-c.) flashed into enucleated eye. Stray light (10 ft-c.) producing ERG on lower tracing in intact eye. Lower tracing shows good on and off potentials, although of lower amplitude than upper because of lower intensity of light. Numbers *1* to *10* refer to number of 15-second intervals since enucleation of right eye. Absent ERG after 120 seconds. Calibration, 50μv. Time, 0.4 second. Up, positive.

tion of the ability of the retina to respond to photic stimulation was tested in these eyes as in the control eyes.

Of the remaining 33 cats, 23 received LSD and 10 received mescaline before enucleation of the first eye. Then, half of each group received pentylenetetrazol and half received strychnine before enucleation of the second eye. Each eye was tested after enucleation as above.

Results

An eye removed from either a cat given pentobarbital or one given curare retains a detectable ERG for two to four minutes (Fig. 2). I shall designate this time as the "viable time." Strychnine prolonged the viable time to 24 to 40 minutes (Fig. 3); mescaline increased it to 8 to 24 minutes; LSD, to 5 to 12 minutes (Fig. 4); atropine, to 8 to 12 minutes. Pentylenetetrazol, epinephrine, and ephedrine did not detectably alter the viable time.

Strychnine given subsequent to LSD or mescaline prolonged the viable time to two hours. Although pentylenetetrazol had no discernible effect alone, if it was given subsequent to LSD the viable time was prolonged to 30 to 40 minutes. Atropine also enhanced the effect of LSD in two animals.

In addition to prolonging the time during which an ERG could be evoked, the drugs strychnine, mescaline, LSD, and atropine had other properties in common. They all induced similar spontaneous potentials in the eyes before enucleation. They all altered the form of the ERG, increasing the a-wave and the b-wave just as hyperventilation does.[4] After enucleation, however, an a-wave never appeared in either the drugged or the control eyes. After administration of the test drugs, the b-wave was sharper and

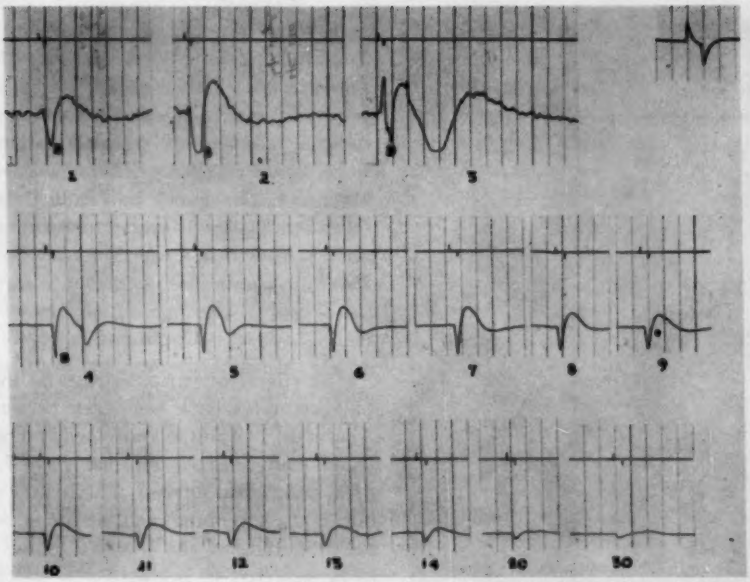
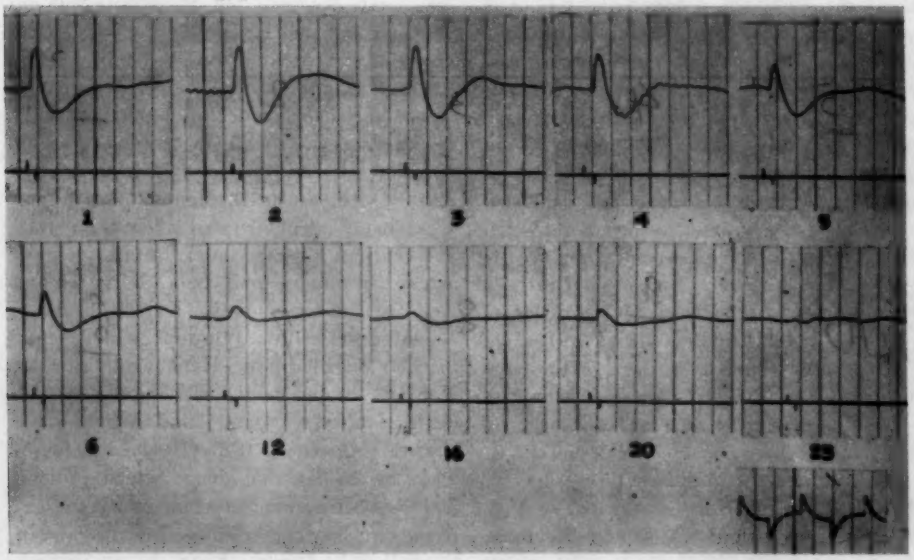


Fig. 3.—*1*, *2*, and *3* show the variations in the b-wave in an intact eye. Records *4* to *14* and *20* and *30* show the ERG from the same eye after the animal has 0.1 mg. of strychnine intraperitoneally and after enucleation. The form of the ERG after enucleation is consistently the same. Numbers *4* to *14* designate the number of 15-second intervals after enucleation. *20* and *30* refer to the number of minutes that have elapsed since enucleation. The ERG is extinguished after 30 minutes. Calibration, 50μv. Time, 0.4 second. Down, positive.

Fig. 4.—Tracing from enucleated left eye of a cat to which 0.05 mg. of LSD was administered i. v. 12 minutes previously. Numbers *1* to *23* refer to number of 15-second intervals from time of enucleation. ERG extinguished after 345 seconds. Record *20* is higher than Record *16* because the stimulus was flashed 45 seconds after a previous stimulus rather than 15 seconds afterward. This apparently allowed better restoration of function of the retina to bring about a better ERG at *20* (300 seconds) than at *16* (240 seconds). Calibration, 50μv. Time, 0.4 second. Up, positive.



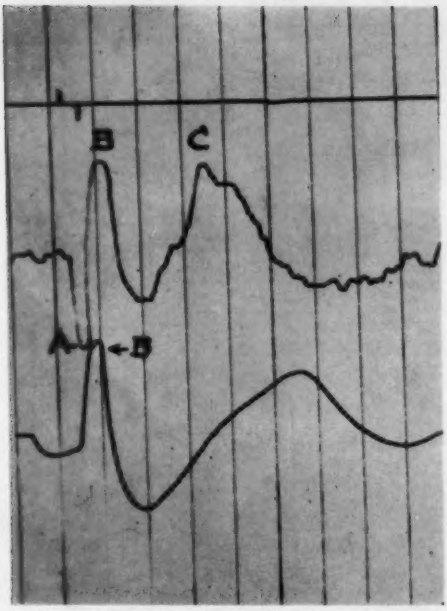


Fig. 5.—Cat had mescaline i. p. 25 minutes before this recording. Upper tracing from intact right eye; lower tracing from enucleated left eye. Complete absence of a-wave in enucleated eye, although it is marked in intact eye. Up, positive. Time, 0.4 second. Amplitude of a-wave, 125μv.

higher than in the control eyes both before and after enucleation. These items are illustrated in Figure 5. The upper tracing shows the evoked response from an intact eye of a cat after LSD was administered. The lower tracing was taken simultaneously from the other eye enucleated five seconds before the record was made. The light flash entered the two corneas simultaneously. In the upper tracing a large negative deflection (a-wave) is present before the enhanced b-wave. In the lower tracing there is no evoked negative wave corresponding to the a-wave. The b-wave is higher than in eyes from cats receiving none of the test drugs.

Another notable finding is that the b-wave is remarkably constant in form after enucleation. Granit [14] has demonstrated that the b-potential may assume a great variety of forms in the intact eye. The potentials *1*, *2*, and *3* in Figure 3 shows this property. The ERG tracings (also illustrated in Fig. 3) after enucleation are similar in form and show no variations except that the amplitude is reduced with each successive photic flash. This lack of variability may be a property of a damaged retina or may indicate absence of normal control from the central nervous system or even from the other eye. It should be recalled that low-intensity flashes to a normal eye produce no a-wave and less variability in the b-wave also.[4]

Comment

The effects of various drugs on the ERG of vertebrates have been well presented by Therman,[32] Granit,[13] and Noell.[24] They have made many discoveries that have been of great theoretical interest. Therman [32] pointed out that strychnine and atropine increase the amplitude of the b-wave. Since others, to be referred to below,[8,11,18-21,27-29,31] have found that the size of the b-wave is reduced in a diseased or damaged retina, it seemed expedient to investigate the power drugs might have to counteract a pathologically reduced b-wave. In this publication I choose to bypass the purely theoretical aspects of the work and to examine the possible practical value of such drugs.

The reduction of the b-wave in asphyxia was first demonstrated by Granit [12-14] on cats and on frogs. Since then, clinical ERG recordings have confirmed the experimental finding. Karpe [19] and Rendahl [28] state that in retinal detachment the b-potential may be used as a rough measure of retinal function. In retinal detachment there is a marked decrease in b-potential. Karpe and Uckerman [21] demonstrated a low b-potential in occlusion of the central retinal vein or artery. In quinine amblyopia (Berggren and Rendahl),[8] siderosis bulbi (Karpe),[20] tapetoretinal degeneration (Straub),[31] and senile macular degeneration (Henkes and van der Kam) [18] the b-potential is reduced. Hyperventilation, on the other hand, increases the b-wave (Alpern).[4] It may be logical, therefore, to assume that drugs which prolong and improve retinal function under the extreme embarrassment induced in the present

experiments might have a beneficial effect on a diseased human retina.

To demonstrate that certain drugs may prolong the viability of an isolated retina is not entirely sufficient. It is necessary to examine the possible explanations for such a phenomenon. Several suggestions should be scrutinized. 1. The drugs may bring about these changes by means of their ability to facilitate synaptic transmission. 2. The drugs may inhibit synaptic inhibitors. 3. The drugs may improve oxygen or glucose supply before enucleation so that the retina has a larger reserve after enucleation. 4. The drugs may sensitize retinal receptors either in themselves or via induced ocular chemical changes. 5. The drugs themselves may be nutrients that are more efficiently and more slowly metabolized than glucose. 6. The drugs themselves may be photoelectrically active. 7. The drugs may induce changes in the electrodes, thereby making the electrodes photoelectrically active.

The seventh possibility may be eliminated, since that particular item was carefully investigated in this study. We found it mandatory to avoid all silver or chlorinated silver electrodes, since they are regularly photically active. Platinum electrodes are not active. After every experiment the electrodes were tested as follows: The contents of the eyes were eviscerated, and the sclera was removed except for the strip which connected the two electrodes. In some cases a potential of 5μv. appeared even though it seemed that all photically active tissue had been removed. A potential of this amplitude is negligible in comparison with the 50μv. to 150μv. responses obtained from the retina. It does, however, indicate that electrodes are always suspect as an innate source of potential. In these experiments the residual 5μv. may be photoelectric in origin or may be induced by the heat generated from the source of light. On the other hand, it may be the result of the movement of pigment cells[16] on the inner surface of the sclera. In any case, it is not related to the action of the drugs, since this small artifact may be found in any eye.

Insofar as the other six possibilities are concerned, none may be conclusively implicated nor may any be positively excluded as the cause of the drug-induced prolonged viability. There are certain facts that should be recalled, however. I shall point out my bias concerning the pros and cons for each suggested possibility.

Treating the first and second guess together, I point out that all four drugs tested are known to affect transmission at certain synapses in the nervous system. Purpura[25, 26] has found that LSD facilitates transmission of an electrically induced action potential at the lateral geniculate body and in some cortical synapses. Rovetta[30] has demonstrated the same action for mescaline. Strychnine is generally considered to act strongly in this way on all central nervous system synapses.[9,17] Evarts,[10] on the other hand, found that large doses of LSD block transmission across the lateral geniculate body of a shock stimulus applied to the optic tract. Atropine also blocks transmission, its action at the parasympathetic nerve endings being its only utilized action. The possibility that these drugs may influence the synapses in the retina has been neglected. It does appear that drugs which lower synaptic thresholds could increase the b-wave.[3] It would not seem logical that this process could be responsible for prolonged viable time, however, unless one assumed that the receptors of the retina were more sensitive to asphyxia than were the synapses. If such were the case, the drugs, not altering the thresholds of the receptors, could allow summation of subliminal receptor impulses at the lowered thresholds of the synapses. This process would result in an enhanced b-wave, both before and after enucleation. It would also increase the length of time that a b-wave would be detectable while the receptors were losing their ability to respond to photic stimulation. Without the drugs, the dying receptor

impulses could not get past the relatively active, but still inadequate, synapses.

The third hypothesis concerns the effect these drugs may have on the oxygen or glucose supply of the retina. Adler [1,2] has shown that the retina may metabolize glucose both aerobically and anaerobically. What is more, part of the retinal supply of glucose is in the vitreous. Since eyes were removed 12 to 20 minutes after administration of the test drugs, it does not seem probable that the glucose supply of the retina or the vitreous could have been measurably increased in so short a time. On the other hand, improved preenucleation oxygen supply could be responsible for the prolonged viability if these drugs do improve blood flow or respiration. Alpern et al.[4] have shown that hyperventilation increases the b-potential. The factor of oxygenation was assiduously studied in the present investigation from two standpoints. Firstly, the successful drugs included strychnine, without circulatory effect, and LSD and mescaline, with circulatory effect. Secondly, the control drugs were all effective circulatory stimulants. It was apparent under the conditions of this experiment that LSD and mescaline do improve cardiac output and respiration depth. However, LSD is more potent on the circulatory system than mescaline, while mescaline is much more potent than LSD on the retina. They do not increase cardiac or respiration rate. Strychnine and locally administered atropine in the doses used had no measurable effect on cardiac rate or efficiency. What is more, ephedrine and epinephrine, which did increase heart rate, had no effect on the viable time of the retina. We must conclude that the successful drugs have properties separate from a circulatory effect in order to produce these results.

A fourth suggestion is that the drugs may sensitize retinal receptors. If this occurred, an increase in the b-wave would result from summation of a larger number of receptor responses [33] rather than from easier transmission of subliminal receptor responses across lowered synaptic thresholds.[3] Neither of these possibilities can be excluded. I should insert here that it is not necessary to assume that all the test drugs have the same mode of action merely because they produce similar results.

As far as the fifth suggestion is concerned, there is no evidence that the drugs may be nutrients or that they may improve the metabolism of nutrients already present.

The sixth suggestion is that the drugs may be photoelectrically active. Axelrod et al.[7] have shown that LSD is intensely fluorescent in minute amounts. In such an instance the present experiments would merely be measuring the concentrations of the drugs in the eye and their rate of breakdown. This would not appear to be a tenable hypothesis, since the intact eye should break down LSD even faster than the enucleated eyes. What is more, none of the other successful drugs are known to be photoelectrically active or fluorescent.

It appears that the drugs LSD, strychnine, mescaline, and atropine successfully improve the action of the retina and aid in its restorative processes in the absence of a renewed blood supply. This property requires further study in order to elucidate its full extent and etiology.

Summary

Seven drugs, strychnine, mescaline, lysergic acid diethylamide (LSD), atropine, pentylenetetrazol (Metrazol), ephedrine, and epinephrine were tested for their ability to prolong the survival time of the retinas of enucleated eyes of 97 cats.

Strychnine, mescaline, LSD, and atropine were successful in prolonging the survival time if they were given before the eye was enucleated. The normal survival time is four minutes. Strychnine increased this to 40 minutes; mescaline, to 25; LSD, to 12, and atropine, to 12. All doses of the drugs were well below the minimal lethal doses.

The ability of the drugs to prolong the viability of the retina paralleled the ability

of the drugs to induce spontaneous potentials in the intact eye.

The success of these drugs appears to be independent of circulatory or respiratory effects.

Pentylenetetrazol, ephedrine, and epinephrine had no effect on the viable time of the retina.

These findings suggest that strychnine, mescaline, LSD, and atropine may improve vision or aid recovery in certain retinal diseases. Preliminary observations on one human subject with macular degeneration are described. In this instance small doses of LSD improved central visual acuity and reduced the size of central scotomas over a 48-hour period. Mescaline has previously been shown to have a similar effect on a diseased retina.

Retinal diseases in which the pathophysiology approaches the experimental conditions of the present study include retinal detachment, macular degenerations, and occlusion of the central retinal vein or artery. Studies of the effects of these drugs on retinal diseases are in progress.

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Secondary Degeneration of the Human Retina

Pathological Study of the Retina in a Case of Secondary Glaucoma and Chronic Uveitis with Use of a New Technique

J. REIMER WOLTER, M.D., Ann Arbor, Mich.

The silver carbonate methods of del Rio Hortega make it possible to visualize normal and pathological structures of the human retina which are not accessible with the conventional histological techniques.[1-4] It is therefore necessary to reexamine with these methods many abnormal situations of the eye the pathology of which has become well known by use of the conventional techniques.

This paper intends to present such an examination of a long-known pathological situation of the human retina: advanced secondary degeneration. It demonstrates the advanced degenerative changes of the retinal neurons and astroglia in a case of secondary glaucoma and chronic uveitis following injury. In this case the silver carbonate methods show the known histological findings in a new light and also enable us to demonstrate completely new pathological changes. The nature and significance of most of these changes is not yet understood, but it is hoped that their detailed description together with that of the clinical picture and of the findings of the routine histological examination may help to deepen our insight into the pathological process in this case and in general.

Case History

A 75-year-old white man was first seen in the ophthalmology clinic on Jan. 10, 1957. He presented a history of having injured his left eye some eight years earlier, with immediate loss of usable vision. The first examination revealed the visual acuity of the left eye to be light perception. There were ciliary flush, corneal edema, and iridodonesis. The slit-lamp examination showed that the lens was not in its normal position and that there were mutton-fat keratic precipitates on the posterior corneal surface and a dense flare of the anterior chamber. Ophthalmoscopy revealed the dislocated lens in a fixed position below. The fundus exhibited old disseminated chorioretinal lesions of a somewhat bone-corpuscle-like arrangement all over the peripheral retina. The optic disc was pale, sharply limited, and clearly excavated. The central retina exhibited no pigmentation, but there was an irregular gliosis and the foveal reflex was missing. The intraocular tension was 49.9 mm. Hg. The right eye was completely normal and had normal vision and a normal visual field. The diagnosis was dislocation of lens, secondary glaucoma, active iritis, and old disseminated chorioretinitis O. S. The treatment was started with pilocarpine, acetazolamide (Diamox), and cortisone.

The patient was seen frequently between Jan. 10 and March 15, 1957. A few days after treatment began the intraocular pressure went down to 8.9 mm. Hg O. S. The pressure remained within normal limits when the eye then was treated with atropine. There was a definite improvement of the condition of the left eye, but it remained irritated and virtually blind. In March a bullous keratitis had developed and the patient decided to have the eye enucleated because of pain.

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From the Laboratories of Neuropathology and Neuro-Ophthalmology and from the Department of Ophthalmology of the University of Michigan.

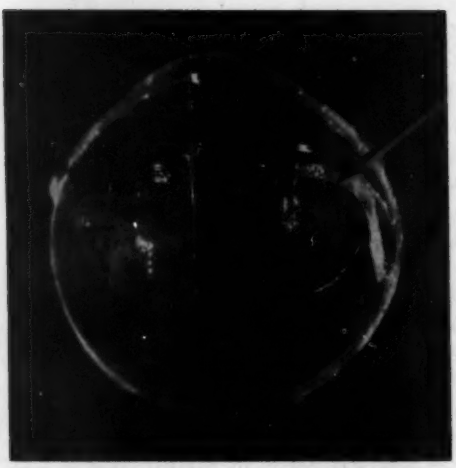

Fig. 1.—Photograph of the inferior half of the left eye that is discussed in this paper. An arrow indicates the position of the dislocated lens. The vitreous is liquefied. The bone-corpuscle-like peripheral pigmentation of the retina is visible.

Method of Histological Examination

Immediately after enucleation the eye was fixed in brom-formalin (Cajal solution). One-half of the eye was embedded in paraffin, cut in serial sections, and stained with hematoxylin and eosin. From the other half of the eye the retina and choroid were removed, and flat sections of both were made on the freezing microtome. These sections were impregnated with the silver carbonate methods of del Rio Hortega.[5]

The figures of this paper represent unretouched photomicrographs.

Results of Routine Histologic Study

Macroscopically the eye was of normal size and shape. The anterior chamber was of about normal depth (Fig. 1). The lens was dislocated and attracted to the peripheral retina and the ciliary body by delicate band-like structures (arrow in Fig. 1). The vitreous was liquefied. The retina exhibited bone-corpuscle-like pigment spots all over its periphery. The center of the retina showed no such pigment spots but looked thicker and whiter than normal. The optic papilla showed some glaucomatous cupping.

The routine histological examination of the eye revealed the following changes: The corneal epithelium was irregular and completely missing in a small central area. There were some small subepithelial bullae. Bowman's membrane was continuous and of normal thickness. The corneal stroma showed slight edema and peripheral infiltration by mononuclear cells. Descemet's membrane was normal. The endothelium was continuous but contained obviously fewer cellular nuclei than normal. There was some chrome inflammation in the perilimbal episclera. The anterior chamber was of about normal depth, and the filtration angle was open. The trabecular system and Schlemm's channel appeared to be well developed and open. The iris was swollen and densely infiltrated with lymphocytes and plasma cells. The ciliary body showed some atrophy and was also chronically infiltrated. The ciliary processes exhibited moderate hyalinization. There was diffuse infiltration with lymphocytes, plasma cells, and histiocytes all through the choroid. Dense, nest-like perivascular accumulations of lymphocytes were observed in some areas of the choroid. The pigment epithelium showed extensive degeneration and some proliferation in the central region of the retina, but it was continuous. In the periphery, however, the pigment epithelium was completely destroyed and most of the free pigment was found in the retina, especially piled up around the blood vessels. The central retina showed an advanced atrophy and gliosis of its inner layers. The outer layers were preserved in their normal architecture. But most of the rods and cones were destroyed, and the remaining ones were swollen and irregular in shape. The peripheral retina exhibited a complete glial scarification, loss of all neurons, and extensive pigment invasion from the destroyed pigment epithelium layer. Newly formed blood vessels extended from the choroid into the scarified peripheral retina and were surrounded by pigment. A new layer of flat proliferating cells could be seen on the inner

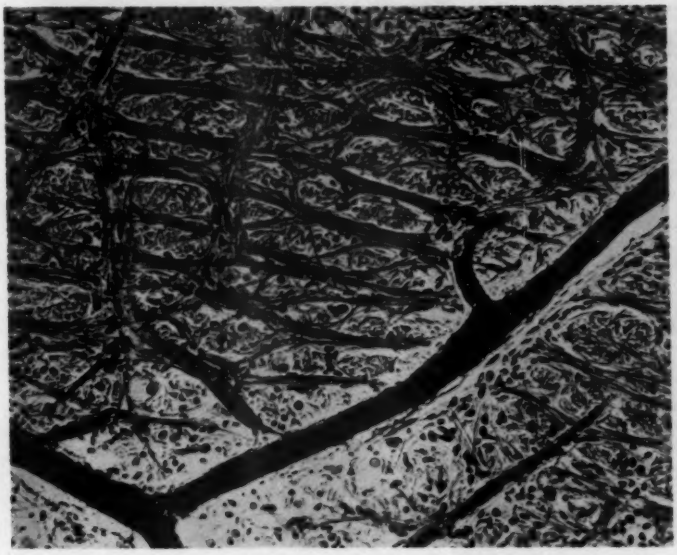

Fig. 2.—Flat section through the inner layers of the central retina which demonstrates a branching artery, the hypertrophic system of astroglia, and the lack of ganglion cells. Photomicrograph, Hortega method; × 200.

surface of the whole retina. This layer was rather thin on the central retina and was especially thick in that area of the retinal periphery where the dislocated lens had been attached. The optic disc showed glaucomatous cupping, and the optic nerve was atrophic. The sclera was normal.

Results of Special Examination of Retina and Optic Papilla with the Silver Carbonate Methods

The silver carbonate stain revealed details of very advanced histological changes all through the retina and optic nerve. These changes were composed of reaction and pro-

Fig. 3.—Flat section of peripheral retina which exhibits the dense scar of hypertrophic astroglia. The hypertrophic astrocytes have relatively large cell bodies and coarse straight processes. Photomicrograph, Hortega method; × 600.

Fig. 4.—Flat section of peripheral retina which exhibits the dense scar of retinal astroglia. The hypertrophic astrocytes have small cell bodies and delicate branching processes. Photomicrograph, Hortega method; × 600.

liferation of astroglia, degeneration and atrophy of neurons, degeneration and new formation of blood vessels, and destruction of the pigment epithelium. In the periphery the choriocapillaris exhibited also extensive destruction.

The glial structures of the central retina exhibited extensive hypertrophy and some proliferation, but as a whole they had retained their normal architecture (Fig. 2). The astroglia of the inner layers of this region surrounded the larger blood vessels with dense glial sheathing and formed a honeycombed system with their long processes (glial fibers), which filled the spaces between the branching blood vessels. This glial system contained and supported the capillary network. The neurons which are normally found in the spaces of the astroglia were almost completely missing, and the remaining cells showed advanced degeneration. Less destruction was found among the neurons of the outer layers of the retina. However, most of the rods and cones were missing, and those which had remained were severely degenerated. The radial fibers of Müller in the central retina showed virtually no pathological changes. The pigment epithelium of the central retina showed some loss of pigment and slight proliferation. But the pigment epithelial layer of this region was continuous and represented a single layer of cells, as it normally does.

In contrast to the generally normal pattern and the moderate hypertrophy of the astroglia of the central retina, there was a tremendous proliferation of the astroglia all through the periphery. This proliferation had resulted in a complete loss of the normal pattern of the retina, and the retinal layers were completely replaced by a dense scar of hypertrophic astroglia (Figs. 3 and 4). This latter scar contained the radial elements of Müller, blood vessels, pigment granula of the destroyed pigment epithelium, and remnants of degenerated neurons. The fibers of Müller were very much distorted but were not seen to participate in this active proliferation of the astroglia.

Different stages of hypertrophy, proliferation, and degeneration of the retinal astroglia were found in the periphery. In some areas the astroglia had relatively large cellular bodies and course straight processes (Fig. 3). In other areas the astrocytes had small cellular bodies and delicate processes which formed dense fibrillar networks (Fig. 4). The astroglia of certain other areas

Fig. 5.—*A*, hypertrophic astroglia with large cell bodies and short branching processes. *B*, similar hypertrophic astrocytes, as in *A*. Two large slightly stained hyaline bodies are seen among the glial fibers without relations to the astrocytes (arrows). Flat sections through the scarified peripheral retina. Photomicrographs, Hortega method; × 700.

Fig. 6.—Flat section through the peripheral retina which exhibits an area of degenerated and hyalinized astroglia. The whole honeycombed structure has become hyalinized, and no individual fibers, cell bodies, or nuclei can be recognized. Photomicrograph, Hortega method; × 600.

Fig. 7.—Flat section through the new layer of hypertrophic astroglia which was found on the inner surface of the retina. Photomicrograph, Hortega method; × 600.

showed very large cell bodies, large nuclei, and relatively short branching processes (Fig. 5, *A* and *B*). In contrast to these proliferative formations, there were also areas of advanced degeneration in some parts of the peripheral retina. There the whole honeycombed network of astroglia had become hyalinized and represented a bizarre structure of hyaline which showed no individual fibers and cellular bodies or nuclei (Fig. 6).

A new layer of proliferating astroglia was found on the inner surface of the whole retina (Fig. 7). The cells of this layer had large bodies and nuclei. Their long processes formed a flat network. This new layer

Fig. 8.—Flat section of the central retina which demonstrates the network of retinal blood vessels. These blood vessels are surrounded by a dense network of hypertrophic astroglia. Photomicrograph, Hortega method; × 100.

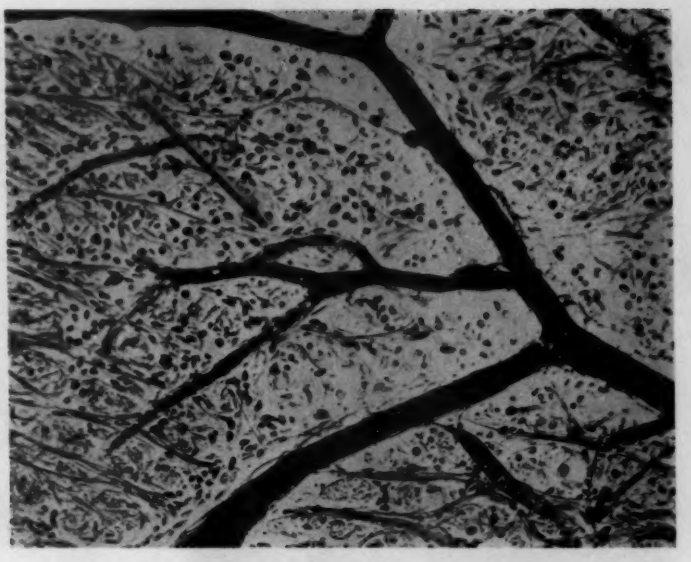

Fig. 9.—A small anastomosis of an artery of the central retina (arrow). Flat section, photomicrograph, Hortega method; × 200.

was relatively thin in the central retina and very thick in the periphery, especially where the dislocated lens had been attached.

The blood vessels of the central retina were of about normal distribution and formed a rather regular network, which was embedded in the hypertrophic astroglia (Fig. 8). In two areas I observed small vascular anastomoses of a peculiar kind, one of which is shown in Figure 9. All blood vessels of the center showed some fibrosis and hyalinization of their walls, but there was no occlusion, and the vessels contained blood.

The blood vessels of the peripheral retina showed very advanced degenerative changes. There were advanced hyalinization, pigment sheathing, and even complete occlusion in

Fig. 10.—Deposition of pigment unrelated to blood vessels in the scarified peripheral retina. Hypertrophic astroglia is seen to surround the pigment. Flat section, photomicrograph, Hortega method; × 300.

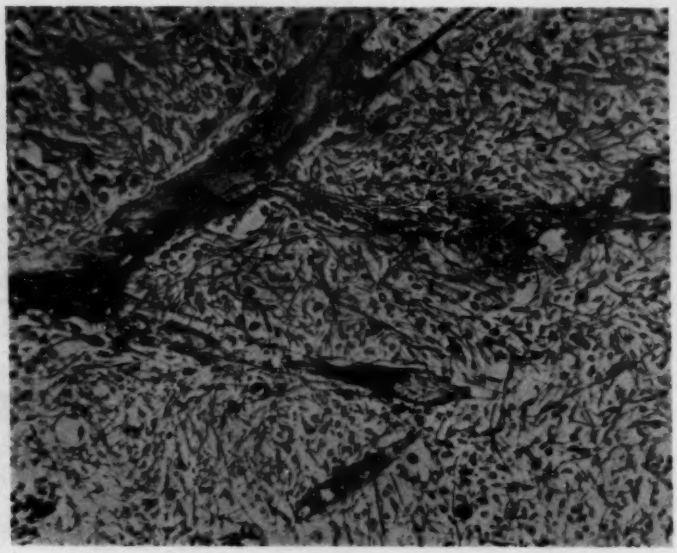

Fig. 11.—Perivascular pigment deposition in the scarified peripheral retina. Flat section, photomicrograph, Hortega method; × 200.

many of them. The pigment sheathing represented an extensive irregular deposition of pigment granules around the more or less degenerated blood vessels (Figs. 11 and 12). Besides the local perivascular accumulation of pigment, there were also slight diffuse deposition of pigment within glia cells and localized deposition without relation to blood vessels (Fig. 10). However, most of the pigment was found accumulated around small blood vessels.

The pigment epithelium of the peripheral retina was found to be completely destroyed. There was no sharp limit between the

Fig. 12.—*A*, degenerated blood vessels of the peripheral retina which exhibits deposition of pigment granules. *B*, hyalinized blood vessel of the peripheral retina which exhibits occlusion and perivascular pigment deposition. Photomicrographs, Hortega method; × 600.

Fig. 13.—A new-formed blood vessel (*d*) extends from the choroid (*b*) into the scarified peripheral retina (*c*). The dark tissue below represents the sclera (*a*). Photomicrograph, Hortega method; × 150.

choroid and the outer retina. The choriocapillaris was missing, and large new-formed blood vessels were found to extend from the choroid into the scarified peripheral retina (Fig. 13). The choriocapillaris of the central retina was well preserved and was filled with erythrocytes.

The neurons of the inner layers of the central retina showed extensive degeneration and atrophy (Fig. 14), and many of them were missing. In the peripheral retina all neurons were destroyed, and their spaces were filled by hypertrophic astroglia. Peculiar hyaline bodies were found in some

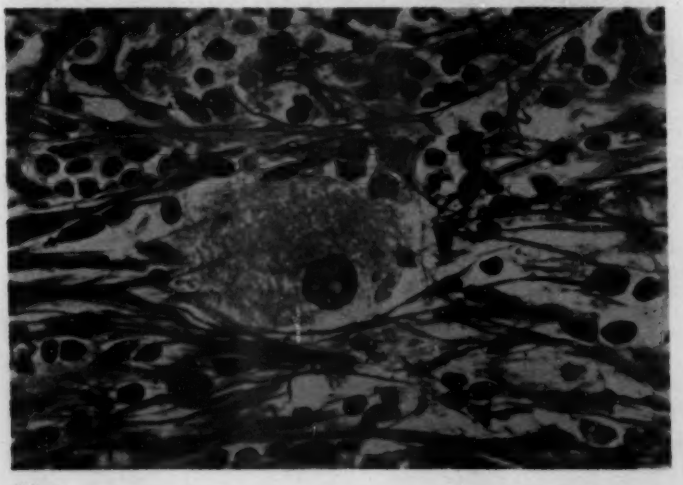

Fig. 14.—Degenerated ganglion cell of the central retina which exhibits swelling, loss of processes, and dissolution of cell body. The cell is surrounded by hypertrophic astroglia. Flat section, photomicrograph, Hortega method; × 600.

Fig. 15.—A single hyaline body within the proliferating astroglia of the peripheral retina. Flat section, photomicrograph, Hortega method; × 600.

areas of this scarified peripheral retina in the place of the missing neurons (Figs. 15 to 18). Most of these bodies were round and measured between 10μ and 50μ in diameter, and many of them showed an onion-like lamellar structure and an unstained center (Figs. 15 and 16). Some of these bodies were irregular in shape and had long processes of hyaline substance (Figs. 17 and 18). These obviously represented hyalinized cells with their processes. It must be emphasized that all these hyaline bodies were observed in areas of the peripheral retina, the astroglia of which showed excessive hypertrophy and proliferation but no signs of degeneration. Regular neurons could not be found in these regions. It is of further interest that the technique designed to stain nerve fibers and ganglion cells resulted in a very good demonstration of these hyaline formations, while there was only very slight staining of these bodies with the technique for astroglia (Fig. 5, *B*).

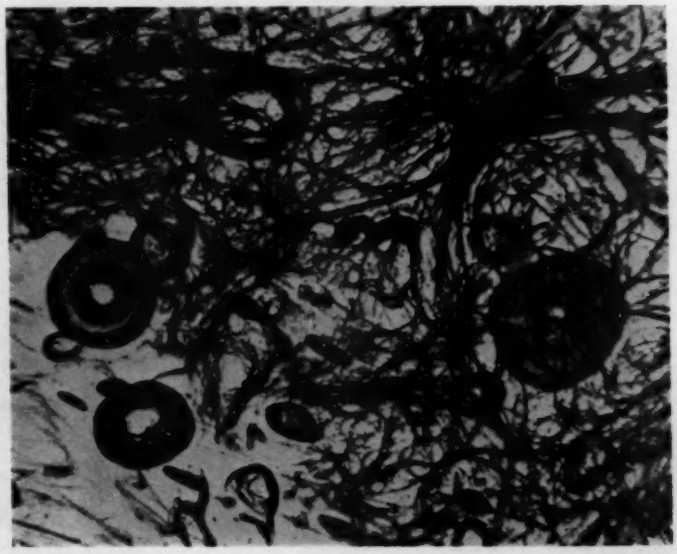

Fig. 16.—A group of hyaline bodies of the peripheral retina. The bodies show an onion-like, lammelar structure and an unstained center. They are surrounded by hypertrophic astroglia. Flat section of peripheral retina, photomicrograph, Hortega method; × 600.

Fig. 17.—Cell-shaped hyaline bodies of the peripheral retina. Flat section, photomicrograph, Hortega method; × 500.

The optic nerve of this case exhibited advanced atrophy, gliosis, and increase of its connective tissue structures. There were some nerve fibers in the optic nerve head. But most of these fibers were interrupted in an area directly posterior to the lamina cribrosa.

The lamina cribrosa showed very extensive hypertrophy of its sieve-like connective tissue structure (Fig. 19). The central blood vessels were small and fibrotic. There also was extensive hypertrophy of the astroglia, which represented a dense scar of astrocytes within the spaces of the lamina cribrosa. Only very few nerve fibers were found to traverse the lamina cribrosa.

The lamina cribrosa was bulged backward in its intermedial parts. Only its peripheral region, which is closely connected with the sclera, and its central part, which is attached

Fig. 18.—Large group of hyaline bodies of peripheral retina within the scar of astroglia. Flat section, photomicrograph, Hortega method; × 500.

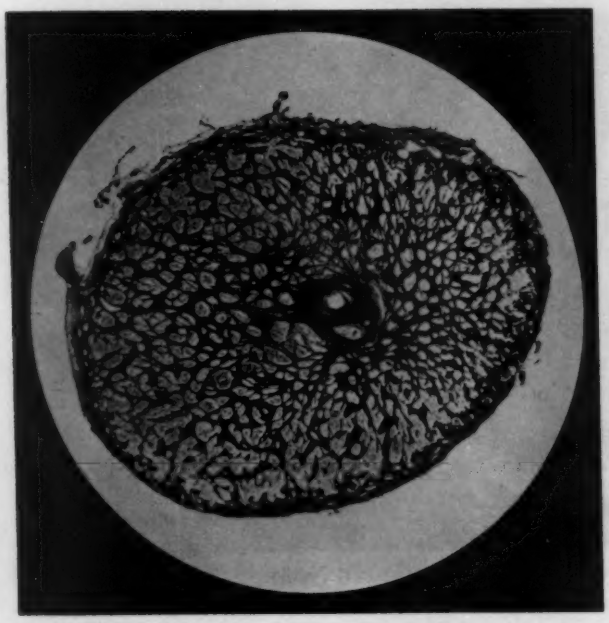

Fig. 19.—Section through the lamina cribrosa of the optic nerve head exhibiting extreme hypertrophy of the connective tissue fibers and narrowing of central vessels. Photomicrograph, Hortega method; × 100.

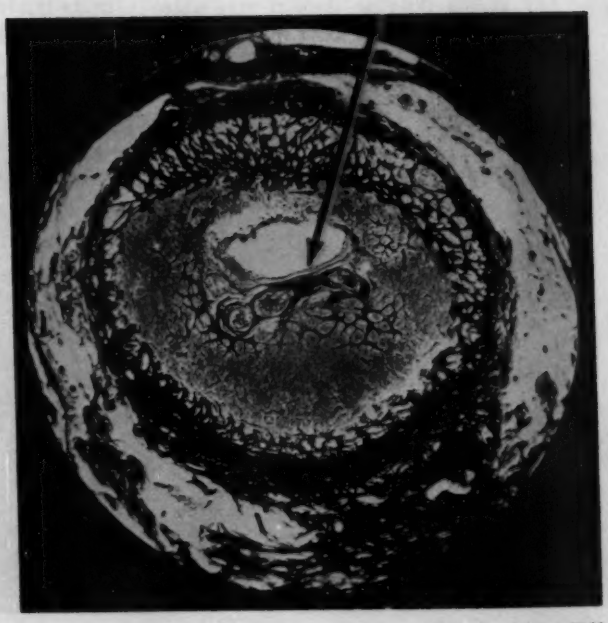

Fig. 20.—Section parallel to Figure 19 at a more anterior level. The lamina cribrosa is bulged backward and takes part in the glaucomatous excavation. The anterior basket-like system of spider cells is compressed into a dense shallow layer of glial fibers (arrow). The nerve fiber layer has virtually disappeared. Photomicrograph, Hortega method; × 100.

to the central vessels, had remained in their normal position (Fig. 20). The anterior part of the optic papilla is normally composed of a wicker-basket-like formation of spider cells and of nerve fiber bundles.[6,7] In this case the basket of spider cells was compressed into a dense shallow layer of glial cells on the inner surface of the excavated lamina cribrosa.

Comment

The essential pathology of the presented case was composed of bullous keratitis, degeneration of the corneal endothelium, chronic uveitis, destruction of the peripheral choriocapillaris and pigment epithelium, advanced degeneration especially of the peripheral retina, glaucomatous cupping of the disc, and optic nerve atrophy. All these changes were nonspecific. The pathology of the choriocapillaris, the pigment epithelium, the retina, and the optic disc were of special interest for this study.

The complete degeneration of all neurons, the proliferation and scar formation of the astroglia, the perivascular deposition of pigment, and the destruction of the choriocapillaris in the peripheral retina as well as the relatively slight involvement of the central retina explained most of the ophthalmoscopical findings in this case. The virtual loss of all neurons of the ganglion cell layer all through the retina accounted for the virtual blindness.

It is the main purpose of this paper to describe the details of the reactive and degenerative changes of the cells of the retina as visualized with the silver carbonate techniques. The anatomy and pathology of the astroglia of the retina is a new field of ophthalmological research. The normal pattern of these cells and some of their pathological reactions have been described only recently.[1,2,8-10] This present case exhibits a multitude of various stages of pathological changes of the retinal astroglia. There were hypertrophy, proliferation, and extensive scar formation. A peculiar degeneration and hyalinization of the whole flat system of astroglia was observed in some areas of the retina. A new layer of flat proliferating astrocytes was found to cover the inner surface of the retina. Such a layer is typically seen in cases of degenerative or old inflammatory eye diseases.[9] I believe that this new layer of astroglia develops by proliferation from some flat astrocytes which seem to be normally present on the inner surface of the inner limiting membrane at the posterior pole of the human eye.[9] This new layer of astrocytes in the present case was probably responsible for the superficial whitish luster which could be seen ophthalmoscopically in the central retina. In all other cases in which I found this new layer of astroglia it was much thicker in the central than in the peripheral retina. In the present case it was just the opposite; the greatest thickness of this layer was found peripherally. This finding can be explained by the fact that the proliferation of these astrocytes probably represents the result of the chronic peripheral irritation of the retina by the dislocated lens. Generally it must be stated that the knowledge of the astroglia of the retina is still much too limited to allow for a complete understanding of the multitude of their reactions found in this and in every pathological eye.

Destruction of the choriocapillaris and the pigment epithelium and invasion of pigment into the scarified retina was found in the periphery of this eye. Most of the pigment granules were deposited around retinal blood vessels, which also exhibited advanced degenerative changes. We are unable to give an explanation for the cause of this severe peripheral involvement and the retinitis pigmentosa-like nature of the retinal changes. This case, however, shows that the pathological changes of the advanced case of retinitis pigmentosa which was recently published in the ARCHIVES[11] are not at all specific for that type of primary retinal degeneration but may also develop under other conditions.

Earlier studies showed that the degeneration of retinal astrocytes[3,11] as well as of

retinal nerve fibers[3,12] may result in the formation of round hyaline bodies (cytoid bodies). The present case exhibited great numbers of such hyaline bodies in the peripheral scarified retina. But there was no degeneration of astroglia. However, many of these bodies clearly represented degenerated cells with their processes. I therefore believe that the hyaline bodies in this case probably represent the end-result of degeneration of retinal neurons. This suggestion does not disturb the current understanding of the development of hyaline bodies in the retina. Heath[13] pointed out that actually any degenerating structure of the retina may become hyalinized and form such hyaline bodies.

It is very interesting to compare the histological findings in the retina of this present case with those in an advanced case of retinitis pigmentosa which was studied with the same techniques.[11] The result of this comparison is that the retinal changes in this case with secondary glaucoma and chronic uveitis are very similar to those of advanced retinitis pigmentosa. In both cases there were virtually the same glial scarification of the retina, destruction of the peripheral choriocapillaris and pigment epithelium, and deposition of pigment granules around the degenerated blood vessels of the peripheral retina. This latter finding undoubtly represents in both cases the histological equivalent of the bone-corpuscle-like pigmentation of the fundus as seen with the ophthalmoscope. Both cases also exhibited peculiar hyaline bodies in the scarified retina. The latter observation of the great similarity of the retinal pathology in the present case and in that of advanced retinitis pigmentosa again indicates that the retinal tissue seem to possess only few possibilities of pathological reaction, which may account for a very similar pathology in different eye diseases. However, there is one difference between the pathology of the present retina and that of the case of advanced retinitis pigmentosa: The degeneration of the retina in the present case had obviously started within the inner retinal layers, while the degeneration in the case of retinitis pigmentosa was found to be more advanced in the outer retinal layers.

The histological study of the optic disc of the present case revealed some interesting facts. It is known that in an adult eye the optic papilla is the only structure of the outer ocular layer which may yield to the increased intraocular pressure in glaucoma. The result is the glaucomatous cupping of the disk. It is obvious in this case of secondary glaucoma that there was not only a backward bulging but also an actual reactive hypertrophy of the sieve-like connective tissue structures of the lamina cribrosa. Another interesting finding is that the intricate basket-like system of spider cells which normally contains the nerve fiber bundles and forms the anterior part of the optic disc was completely compressed in this case, obviously as a result of the increased intraocular pressure. Both facts contributed in this case to the formation of an extensive glaucomatous cup.

It is my hope that this case report may help to initiate new interest in histological details of the cellular reactions of the human eye. An understanding of these cellular reactions is important, since all of them together actually determine the nature and course of an eye disease.

Neuropsychiatric Institute, University Hospital.

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On Improving Retinal Photographic Standards

Film Selectivity with Use of the New Carl Zeiss Retinal Camera

HERMAN J. NORTON Jr., M.D., and CHARLES T. SULLIVAN, M.D., Rochester, N. Y.

The two sections of this paper will deal with significantly practical developments in new color-film production and with optical-illuminating advances as exemplified by the new Carl Zeiss Fundus Camera. Suggestions will be made relevant to applying the combined developments in a maximally meaningful way, the prime objective being to improve the caliber of retinal photography.

Retinography and Film Choice

The text of this section will be based directly upon the accompanying Table. The conclusions and information discussed in the following compendium are based on studies conducted by us. Although seven color films have been listed, only five were actually used during the calibration studies. Two German films, not yet available, have been included in order to present a complete list of 35 mm. color films.

Film exposure index, expressed in ASA units, is a yardstick of the sensitivity of a film to light. A review of the literature reveals that slow or relatively insensitive film, particularly in the case of color, was a major obstacle encountered by the pioneer retinal photographers. Although intense light sources were available first by harnessing sunlight itself and then by the use of the open carbon arc, followed by overloading a tungsten-type source, records show that the shutter of retinal cameras had to be open for 0.2 to 0.5 second to expose color film properly. Obviously this is a considerably longer time than it takes for the fastest phase of the blink reflex to take place, such lid motion thus being a source of interference in obtaining good retinal pictures. Even with such long exposure times necessitated by the low light-sensitiv-

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From the Department of Surgery, Division of Ophthalmology, of The University of Rochester Medical Center.

Characteristics of Thirty-Five Millimeter Daylight Color Films with Various ASA Ratings (Zeiss Retinal Camera Light Source)

	Exposure Index, ASA Rating	Flash-Tube Intensity and Diaphragm Aperture *	Fundus Color Fidelity & Comments	Resolving Power (Lines per Mm.) and "Acutance"
Reversal Type				
1. Kodachrome	10	I to II, semicircle	Retinal color authentic except for disc, which reproduces too white; film of choice for fine retinal lesions	90, "acutance" 3 times that o Ektachrome and Kodacolor
2. Ektachrome	32	I, slit	Retinal color and nerve well reproduced; first choice for gross retinal lesions	80; "acutance," see Kodachrome
3. Anscochrome	32	I, slit	Similar to Ektachrome; color is softer; slight tendency toward brown in retinal color	50; "acutance" similar to Ektachrome
4. Agfacolor CU-18	40	I, slit (anticipated)	Unknown at present time	Not yet available
5. Superanscochrome	100	I, slit	Overexposed even with least light; place in retinal photography not yet definite	50; "acutance" similar to Ektachrome
Negative Type				
6. Kodak Negative (Kodacolor)	25	I, semicircle	Film of choice for blood vessel and vascular lesions; retinal color tends slightly toward brown	55; "acutance," see Kodachrome
7. Agfacolor CN-17	32	I, slit (anticipated)	Unknown at present time	Not yet available

* The Roman numerals refer to flash-tube intensity settings on the camera control gear. The designation following the numeral refers to the illuminating diaphragm aperture of the camera. Together these two adjustments determine the intensity and amount of light entering the optical system of the camera. Notations in other columns are considered in the text.

ity of films, overexposure of retinal photographs has been uncommon in the past.

Overexposure, therefore, has not been a particularly important factor contributing to poor retinal photographs to date. Today, however, it can play an increasingly important role in contributing to unsatisfactory photographs of the retina. The reason for this is twofold: (1) increased film sensitivity and (2) more efficient point light sources. The first two columns of the Table summarize our experience in making available all present-day information relevant to 35 mm. film sensitivity as it is affected by the illuminating system of the new Zeiss Fundus Camera. The first tabulation indicates that color film sensitivity now falls between 10 and 100 ASA, the smaller figure representing least and the the larger figure, the greatest sensitivity, under normal processing schedules. There is a tenfold increase in sensitivity over that of older films. When these sensitivity ranges are calibrated with the electronic flash tube in the new camera (Table, Column 2), the general outcome is that all will be overexposed if the highest-intensity lamp discharge is used with the widest illuminating diaphragm of the camera. In the case of five films the lowest discharge intensity coupled with the smallest diaphragm opening, the slit, must be used to obtain proper exposure, with use of normal processing routines. Superanscochrome film, which has an ASA rating of 100, is overexposed even when lowest intensity of discharge and least amount of light is involved. Further studies involving this film will be required to fully evaluate its place in retinal photography. The full effectiveness of the intense light source used in the new camera is appreciated when it is realized that the slowest color film can be readily overexposed.

The second interest in this study was to determine how well the various films actually reproduce the true color of the structures composing the human ocular fundus. In addition, it was postulated that certain physical differences between the films such as the "acutance," or "contour sharpness," and film resolving power, or resolution, might make it efficacious to choose one film over another, depending upon the type of lesion involved and upon its location within the eye, e. g., nerve, macula, blood vessels, or retina proper. The last two columns in the Table summarize in brief form our experiences to date along this line.

Thirty-five millimeter Kodachrome film was available about 20 years prior to the appearance of some of the other color films listed. For this reason, 35 mm. color films are compared with this early miniature-type film as a control. Our work to date has revealed the following color considerations regarding photography of the internal structures of the human eye. The normal color of the optic disc is considered to be a pinkish-white. Kodachrome whites are "bluish-whites," which means that this film tends to reproduce an extreme "porcelain-type" white. In the case of the optic nerve head such documentation is unfortunate, for a normal nerve head may be recorded as atrophic under such a condition. Support for this viewpoint can be given by merely reviewing retinal photographs taken with this film and noting how frequently it would be justifiable to make a diagnosis of optic atrophy from the photograph, such a diagnosis being proven incorrect by correlating the picture impression with the facts of the case record.

Just as one color extreme means optic nerve pathology, so too can another color overaccentuation indicate the presence of disease. Where the above-mentioned film tends to overemphasize the white element of the normal optic disc, negative-type color film unduly accentuates the pink component of the normal disc color. In such a case one might legitimately conclude that hyperemia or early optic neuritis was present when in reality the nerve was normal. Since optic disc pathology not infrequently manifests itself as a deviation from a certain

normally accepted color, accurate rendition of the normal disc color is of the utmost importance. We next turned to Ektachrome film in the comparative film studies. Evidence indicates that this film reproduces the color of the normal disc, as well as color deviations of pathological discs, more authentically than other films. Ektachrome whites are "yellow-whites," in contrast to the "bluish-whites" of Kodachrome. Relevant to the optic disc this means that the former reproduces the normal color of the disc with more complete fidelity than the latter. Support for this judgment is best given by a side-by-side comparison of the optic disc color in two photographs, one having been made on Kodachrome and the other on Ektachrome film. Anscochrome film is very similar to Ektachrome, but its color is somewhat softer and because of this might be considered to interpret nature more accurately. It is our feeling at this time that Ektachrome and Anscochrome are the films of choice when the physician is trying to record the normal and/or abnormal color of the optic disc in the most photographically accurate way.

To date experience indicates that a 35 mm. negative-type color film such as Kodacolor reproduces most authentically retinal vascular and blood vessel lesions. An unsurpassed contrast between artery and vein as well as between a retinal hemorrhagic area and surrounding normal retina is apparent with this film. Accentuated arteriolar reflexes and arteriolar-venular compression can be very accurately recorded. After comparing the appearance of the retinal vascular tree as photographed on this film with its appearance on another film, very little doubt remains as to the proper film selection for recording retinal vascular pathology.

Resolving power or resolution of a film refers to its ability to separate so many fine lines per millimeter. It is a numerical measure. "Acutance," or "contour sharpness," is a non-numerical measure or way of describing the abruptness with which the image of an object and its background separates from each other. When an image outline is distinct and does not tend to merge with its background the "acutance" is high, whereas the reverse is true when "acutance" is low. Resolving power and "acutance" are important concomitants of sharpness, the concept of "acutance" being of somewhat greater significance. Because of the importance of film sharpness in distinguishing minute pathological change of the retina, it was decided to include, as shown in the Table, information relevant to resolving power and "acutance" of the films under investigation.

Study of the Table reveals that Kodachrome film leads the list, having a resolving power of about 90 lines per millimeter and an "acutance" approximately three times greater than Ektachrome or Kodacolor film. It is these qualities that make Kodachrome the film of choice when one is photographing very fine pathological change of the retina, where contrast in the lesion may be low. When pathology is characterized by very slight change, the proper film for recording such change is one with a maximum power of resolution and a high image-background contrast. Examples of such change are fine stippling or granularity in the macular region, fine neovascularization of the retina and disc, and fine pin-point hemorrhages and microaneurysms of the retina.

Optics and Illumination

The second section of this paper will be concerned with those new optical and illuminating principles which have not heretofore been an integral part of retinal cameras. The discussion to follow is based on Figures 1 and 2.

The immediate aim of the optical-illuminating system of the new Zeiss retinal camera is to place an intermediate image of the light source in the patient's pupil, while the ultimate objective is to project a 30 degree, 22 mm. in diameter, intermediate image of the ocular fundus, having a constant $\times 2.5$ magnification, regardless of the patient's ametropia and/or accommodation, on to 35 mm. film, the exposure being free

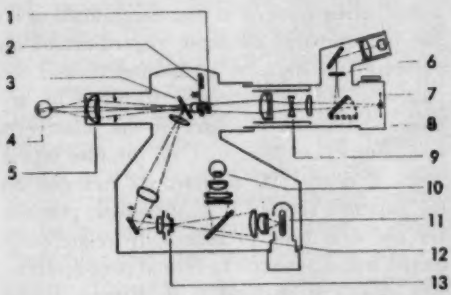


Fig. 1.—Diagram showing the optical-illuminating system of the new Zeiss camera. (*1*) Spherical correcting lens; (*2*) astigmatic correcting elements; (*3*) mirror; (*4*) patient's eye; (*5*) aspheric ophthalmoscope objective; (*6*) diaphragm; (*7*) film plane; (*8*) reflex mirror; (*9*) photographic objective; (*10*) tungsten focusing lamp; (*11*) electronic flash tube; (*12*) mirror surface; (*13*) illuminating diaphragms. (Reproduced with permission from Carl Zeiss, Inc., New York.)

from astigmatism. Such an accomplishment permits the photograph to be used in a quantitative way, making it possible to correlate the size of visual field lesions with retinal photographic pathology.

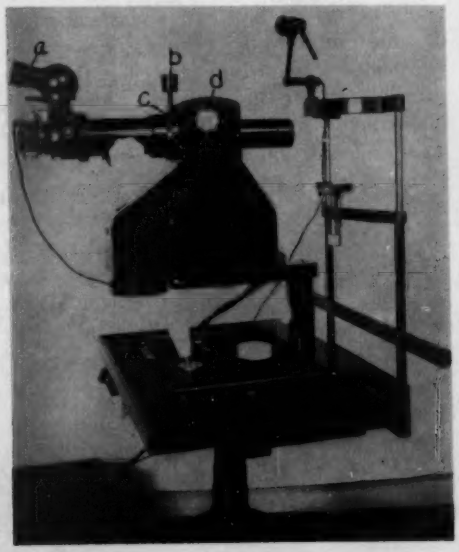
That the reader may more fully comprehend the accomplishment mentioned in the above paragraph as well as thoroughly understand an instrument of this caliber, the following general account of the optical-illuminating system is offered. In brief, the light pathway through the new camera which leads to the ultimate aim mentioned above is as follows: The tungsten light source (*10*, Fig. 1), is used during the focusing period, while the electronic lamp source (*11*) is used to supply sufficient concentrated light for making the exposure. Light rays from the flash source (*11*) penetrate a condenser system and pass through a glass plate (*12*), while rays from the tungsten lamp (*10*) are reflected by the glass plate (*12*). An intermediate image, a ring of light, of each light source is formed at the plane (*13*). It is at this point that diaphrams can be interposed which control the amount of light entering the system. Through three more objectives and a mirror surface, all shown in Figure 1, the intermediate image of the light source is reproduced on the mirror plate (*3*). The wide-angle aplanatic ophthalmoscope objective (*5*) projects the reproduced intermediate image of the light source on to the pupillary plane of the patient's eye. In like manner, the ophthalmoscope objective projects the intermediate image of the subject's retina in its focal plane when the patient's eye is emmetropic or when it is made emmetropic by the spherical correcting lens (*1*) and/or the astigmatic correcting lens (*2*). After the retinal image of the patient's eye penetrates the photographic objective (*9*), it is projected either on to the film plane (*7*) or in the image plane of the observation eyepiece (*6*), depending upon the position of the reflex mirror (*8*).

Three control features in the new optical system deserve particular amplification, for they represent optical advancements which, with the film considerations introduced above, might reasonably be expected to set retinal photographic standards for the next several decades. These new controls are represented by *1*, *2*, and *13* in Figure 1. First, *13* represents the plane where the intermediate image of the light source is formed. This is in the form of a ring of light, or for descriptive purposes, is a spot of light with a dark central zone which is really devoid of rays. In a classical paper on the subject of centric photography Nordenson [1] beautifully describes the basic principles underlying this type of retinal illumination. Perhaps the more practical significance of this system of retinal illumination is the fact that various illuminating diaphragms can be interposed into the system at *13*, thus modifying the full ring of light through three smaller-sized light rings to a semicircle, oval, and slit. In this way a very sensitive control of the illuminating system is afforded, providing "custom-type" illumination for the particular eye undergoing photography. The widest light ring permits the greatest while the slit form permits the least amount of light to enter the system. These various light-governing diaphragms are controlled by a knob, not

shown in Figure 2, located on the left side of the camera. The amount of light entering the system is controlled, therefore, at this point, while the intensity of the light source for the system is determined by a four-way switch located on the control gear for the unit. The diaphragm setting together with the control gear intensity position were used in calibrating the films considered in the first section of this paper (Table).

The second and third features new to a retinal camera optical system are represented by *1* and *2* in Figure 1. These two positions are represented externally by *b-c* and *d*, respectively, in Figure 2. The knob marked *d* controls a set of correction lenses which convert an ametropic to an emmetropic eye, spherically speaking, prior to photography. Under such a condition the ophthalmoscope objective (*5*, Fig. 1) produces an image of the retina at its focal plane. Telecentricity is the term applied to this mechanism. The practical significance of this advancement is that it makes the unit a measuring camera in that magnification on the film remains constant, regardless of an existing ametropia or accommodation of the patient's eye or improper focusing or accommodation on the part of the observer's eye. For example, 1 mm. on the film represents 1 degree 20 minutes±2 minutes on the patient's retina. It is, therefore, possible for the first time to accurately relate perimetric measurements to retinal photography. The positions marked *2* in Figure 1 and *b-c* in Figure 2 correspond to two astigmatic objectives which can be rotated against each other as well as together in either direction. These elements have a cylindrical effect which corrects the astigmatism in the patient's eye, a particularly important consideration when a photograph of the retinal periphery is contemplated. The scale marked *a* in Figure 2 represents the reticle in the eyepiece of the camera. This must be individually set by each observer. The cross hair in the ocular must be adjusted so that it is simultaneously in focus with a small retinal vessel before an exposure is made. Other camera features shown in Figure 2, but not labeled, are felt to be self-explanatory, and no attention will be given to them in this communication.

Fig. 2.—External appearance of the new Zeiss camera. Only these completely new features are labeled and discussed in the text. (*a*) Ocular focusing reticle; (*b*) knob for correcting cylindrical error of patient's eye; (*c*) scale for setting axis of correcting cylinder; (*d*) wheel for introducing spherical correction.



Although the use of an electronic flash tube is not a new feature in retinal photography, having been introduced in 1953 by Ogle and Rucker,[2] there are new features to the positioning of the two light sources in the new camera. The above investigators presented a flash-tube adaption for the Zeiss-Nordenson camera, but unfortunately they encountered the phenomenon of film reciprocity failure, necessitating special processing service, which decreased the practicality of their contribution. Two years later one of us (H. J. N.) [3] described the use of an electronic flash tube with which proper exposure could be obtained, following normal processing procedures. Ogle and Rucker used multiple rapid low-intensity discharges of the flash tube for preexposure focusing purposes. This method can be annoying to both patient and observer

and, in addition, decreases the life of the costly flash tube. Norton used a flash tube for exposing and a tungsten lamp for focusing mounted in tandem, the tube above the lamp. In this way the life of the tube was prolonged considerably and the focusing period proved to be less disturbing. Even though two separate light sources proved to be a definite advantage over a single flash tube used for both focusing and exposure, the new camera under discussion here adds still a further refinement by providing separate mounting positions for the two lamps, as indicated in Figure 1. This arrangement has certain technical advantages for both the focusing and exposure periods which will not be discussed further at this time.

It has been estimated, on the basis of fundus color fidelity studies using several daylight-type color films, that the color temperature of the flash tube falls between 5500 and 6500 degrees Kelvin. The 50-watt 110-volt tungsten lamp is used only for focusing purposes. Unlike the situation in the past, camera shutter speeds are no longer of concern. The shutter of the Contax camera housing is set at 0.02 second, and the flash-tube discharge lasts less than 0.006 second. From these figures it is clear that the latter figure, rather than the length of time the camera shutter is open, determines the speed with which the exposure is made. This is in considerable contrast to the Zeiss-Nordenson and other units in which the length of time the camera shutter is open controls the rapidity with which the exposure is made. The ultrarapid discharge of the flash tube determines the exposure speed, and in this case it is several times faster than the fastest, or down, component of the blink reflex as recorded by Hartridge.[4]

Lastly, through a special marking device and identification cards it is possible to label the film photographically. The principles and advantages of photographic labeling of valuable medical slides has recently been considered by one of us (H. J. N.).[5]

Comment

There seems to be little doubt that through the use of a retinal photographic unit capable of quantitative measurement based on the newly introduced optical control features considered above, coupled with proper film selection for the particular type of pathology involved, the caliber of retinal photographic recordings will improve.

The approach to retinal photography introduced in this communication is intended to be a challenge to ophthalmologists interested in this subject, some of whom may contribute further in this direction and, therefore, aid in improving retinal photographic standards.

Summary

Consideration is given to the subject of improving retinal photographic standards through a knowledge of the technical characteristics of several 35 mm. color films. The reactions of these various films to light as it is produced by the optical-illuminating system of the new Carl Zeiss Fundus Camera are studied and tabulated. Conclusions and suggestions are made relevant to the films of choice for recording various types of retinal lesions.

Remarkable new optical features not heretofore intrinsic in retinal cameras are considered, and their practical value is briefly discussed.

797 Elmwood Ave. (20).

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A Suturing Spatula

CONRAD BERENS, M.D., New York

In inserting sutures to unite corneal or scleral wounds in cataract extraction, in lamellar scleral resection for retinal detachment, in affixing a donor corneal graft, and in other ocular surgery it is important to facilitate the introduction of the needle and to minimize trauma and displacement of tissues.

A suturing spatula * has been devised (Figure) which facilitates the introduction of the needle and passage of the sutures through the tissues.

The instrument is 100 mm. in length, with a flattened spatula-like expansion at each end, curved to fit the contour of the eyeball. There are several angular notches which may be placed against the point of exit of the needle and holes which may be placed over the needle point for exerting counter-pressure. A channel through which the suture may be removed is made in the ring surrounding each hole.

A suturing spatula to facilitate the introduction of the needle and the passage of sutures through the tissues in cataract and corneal surgery and scleral resection for retinal detachment.

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* Made by Storz Instrument Co., St. Louis.

708 Park Ave.

Annual Reviews

Diseases of the Retina and Optic Nerve

ROBERT W. HOLLENHORST, M.D., Rochester, Minn.

Since the publication of the last annual review of diseases of the retina and optic nerve [1] an extremely large number of articles has appeared. Many of less importance had to be omitted, and, of course, not all were found that appeared in the literature. Important papers published prior to the last annual report and located through abstract journals are included. I have reviewed those articles I believe to be of general interest.

Drews [2-5] published a series of articles pertaining to fundus photography with use of an electronic flash source of the flicker-flash type adapted to the Nordenson fundus camera. Liesenfeld [6] photographed the fundus through the electric ophthalmoscope by using a Minox camera with a special mirror device. Arkin [7] replaced the ocular of a Gullstrand ophthalmoscope with a Kine-Exakta camera using a specially designed bulb.

Bedell [8] illustrated a talk on various lesions of the fundus with his beautiful photographs of the fundus. Goldmann's [9] lecture on slit-lamp microscopy of the vitreous and fundus is an interesting and lucid description which is well worth reading in its entirety.

Retrolental Fibroplasia

There has been a sharp decrease in the number of articles on retrolental fibroplasia. This apparently reflects the reduced incidence of the disease following upon careful regulation of the administration of oxygen to premature babies. Banister and Locke [10] stated that sporadic cases of retrolental fibroplasia are still occurring in spite of the knowledge that control of oxygen is necessary. In not one of their 126 infants weighing 4 lb. or less at birth were even the mildest manifestations of the disease observed. They said that the disease can be completely prevented by following control measures as outlined in their article. Eliasoph [11] discussed thoroughly some physiologic and developmental data which should be read in the original in his article. Two papers [12,13] discussed the remarkably reduced incidence of retrolental fibroplasia among premature infants recently receiving curtailed oxygen administration as compared with those prior to 1954 who received oxygen unrestrictedly. Two papers [14,15] state that either corticotropin (ACTH) or the adrenal cortical steroids may be of benefit in cases of this disease.

An interesting paper by Gregory [16] concerns 30 children affected by retrolental fibroplasia but not totally blind. Myopia ranging from −2.5 to −18 D. was found in 85% of the cases. Of the children with useful vision, 50% had nystagmus. Fourteen had unilateral microphthalmos, and the affected eye usually was amblyopic and deviated nasally. Seventeen children (approximately 60%) had strabismus, which, in all but one, was esotropia. Two-thirds had vitreous opacities, and one-half had malformations of the optic disc. Most of the patients had large areas of scar and pigmentary changes in the fundi. Fourteen patients had small localized detachments of the retina, and five had retinal folds. Hirose

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Section of Ophthalmology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

and Yoshioka[17] examined the eyes of 15 anencephalic fetuses. Three of the thirty eyes had retrolental fibroplasia. Only these three fetuses had delayed physiologic degeneration of the fetal zone of the adrenal glands. This led the authors to postulate for retrolental fibroplasia a possible congenital origin as opposed to a postnatal origin. Tayebi[18] noted radiologically demonstrable calcification in 19 eyes out of 41 affected by retrolental fibroplasia. He therefore considered calcification an unreliable differentiating feature from retinoblastoma.

Gibbs and associates[19] obtained electroencephalographic recordings on 51 patients who had retrolental fibroplasia. Twenty-seven per cent had some form of clinical epilepsy. Seventy per cent of those without epilepsy had seizure activity in their recordings. Those 3 years of age or over had a higher incidence of such seizure activity. The following are possible causes of the seizure activity in retrolental fibroplasia: transsynaptic degenerative changes in the brain secondary to blindness in early infancy, oxygen poisoning of the immature brain resulting from excess oxygen in the respired air, and premature photic stimulation.

Several papers deal with other changes occurring in the eyes of premature babies. Kästner[20] noted among 130 infants only 1 child with partial retrolental fibroplasia. Most of these babies had a lowered secretion of tears, and this was thought to explain the occasional poor visibility of the fundi of premature babies. MacDonald and Wilson[21] called attention to the grayness of the peripheral fundus of premature infants. They observed a very fine pigmentation of the fundi among some 25% of these children up to the age of 2 years. The incidence of retinal hemorrhages in newborn children ranges from 18% to 45% in the reports of various authors.[22-26] The percentages are much higher among infants delivered by difficult labor or by expressive measures. Eleven per cent of infants delivered by cesarean section had retinal hemorrhages.[22] Several of these authors recommend vitamin K administration prior to parturition. Lomíčková and Otradovec[26] have expressed the belief that fetal hypoxia is an important factor in the etiology of these retinal hemorrhages.

Experimental Studies.—In contrast to former years, reports of experimental procedures are few and have come from two laboratories. Pedler[27] described in detail the pattern of the lighting system, the animal chamber, the microscope, the cinecamera and the control gear used by Ashton and his co-workers in their studies on retinal blood vessels. The technique involves removal of the anterior ocular structures including the lens and replacement of these with a transparent window through which the observations are made. Pedler[28] also reported that Co^{60} radiation produced no abnormal reaction in the retinal vessels of kittens. He concluded that the animal's biochemical system, known to be affected by irradiation, is not involved in the vaso-obliterative reaction.

Ashton[29] discussed the constrictive effect of oxygen on new capillaries and noted that he had found no other metabolic changes in the retina, such as disturbed oxygen consumption, anaerobic glycolysis, or succinic dehydrogenase. Ashton and associates[30] hypothesized that the closure of the retinal arterioles might be due to external pressure from fluid imbibition by the retina as a result of an interruption in glycolysis. They therefore investigated the action of sodium fluoride and sodium iodoacetate, both glycolytic inhibitors. These substances produced total obliteration of the retinal vessels of kittens similar to that induced by exposure to oxygen. The effect did not occur in the retina of the adult cat. The vessels reopened when the retina became detached from the choroid. Whether the mechanism of oxygen vaso-obliteration is related to these findings or not is as yet unknown.

Patz[31] presented a complete paper on this entire subject at the time he was awarded the E. Mead Johnson scroll. Patz and Eastham[32] demonstrated that gradual withdrawal of young mice from an initial

high concentration of oxygen did not prevent ocular lesions from developing. They observed [33] that gradual withdrawal actually increased both the severity and the frequency of ocular lesions. They found that the eyes of newborn mice were not injured by exposures to 30% concentration of oxygen but that a 40% concentration became harmful after exposure for periods ranging from 7 to 10 days. Kinsey,[34] in commenting on this paper, stated that retrolental fibroplasia may develop in premature infants even when an oxygen concentration of 40% is not exceeded. Szewczyk [35] said that the changes were those of hypoxia and not of oxygen toxicity and that the infants should be withdrawn from oxygen slowly if it had been administered previously.

Retinopathy in Diabetes

Several excellent monographs that review the entire problem of diabetes and its effect on the eyes have appeared in the world literature. These include the papers by Thiel,[36] Palomar Palomar,[37] Forster,[38] Alaerts and Slosse,[39] and Ashton.[40]

Janert and associates,[41] in the second part of a report on 2600 controlled diabetic patients, noted that one-third had retinopathy. Retinopathy was rare before the age of 20. The retinopathy was severer among those whose diabetes arose in early life. The authors expressed the belief that cataract and retinopathy due to diabetes have different causes. Sauer [42] found that poor diabetic control increased the incidence of retinopathy and vascular complications. Palich-Szántó and Bikich [43] found similar data in their series. Fischer [44] reported on nine patients whose diabetes started after the age of 50 and in whom, in spite of this late onset, proliferating retinitis developed. Hardin and associates [45] studied 140 well-controlled juvenile diabetics whose disease had been present at least 15 years. They found a highly significant correlation between the degree of control and the severity of retinopathy but no relation between the duration of diabetes and the severity of retinopathy. Joss and Johnston [46] and Heinsius [47] studied the incidence of diabetic retinopathy among patients whose diabetes appeared during childhood.

Paufique [48] reported on five patients of whom four had retinal and one had vitreous hemorrhage with no obvious cause. All had a normal concentration of blood sugar and had no glycosuria, but the glucose-tolerance test showed disturbed metabolism of sugar. All hemorrhage absorbed when a strict diet was followed. Falzoi and associates [49] studied the renal function of 25 diabetics with retinopathy and found no correlation between renal dysfunction and severity of retinopathy. Klein and Bressler [50] reported two cases among diabetics in whom there was optic atrophy in one eye and papilledema in the other. Neither patient had a space-occupying lesion of the skull; in one, the lesions of the optic disc could be attributed to diabetic neuropathy, but in the other the cause was unknown. Tunbridge and Paley [51] reported on two siblings who had juvenile diabetes, marked conduction-type deafness, and primary optic atrophy. These lesions probably were unrelated to diabetes but were manifestations of hereditary primary optic atrophy.

Pathologic Physiology.—Kornerup [52,53] investigated the blood pressure of 1285 diabetic patients. He found that diabetic retinopathy and rise of blood pressure were closely correlated parallel phenomena but were two distinct manifestations of the vascular disease typical of diabetes. Maengwyn-Davies and associates [54] postulated that diabetics without retinopathy possess a zona fasciculata of the adrenal cortex that is less active than in the normal person, whereas diabetics with retinopathy possess an overactive one. They found that patients with retinopathy excreted a significantly larger amount of urinary 17-hydroxycorticosteroids in 24 hours than did diabetic patients without retinopathy. The diabetic group as a whole showed a smaller urinary excretion of steroids after an oral test dose of hydrocortisone than did normal controls.

Lerman and associates [55] found that diabetics with retinopathy have a significantly increased concentration of α_2-globulin in the serum, but that the α_2-globulin levels of diabetics without retinopathy are the same as in normal controls. A significant elevation of serum α_2-globulin developed in alloxan-diabetic rabbits given a three-week course of cortisone, and in 80% renal lesions of the Kimmelstiel-Wilson type developed. The levels of serum glucosamine were elevated in all diabetic patients, but there was no difference between those who had and those who did not have retinopathy. Lerman [56] briefly discussed the more recent advances in the elucidation of the causes of diabetic retinopathy. He noted the effect of corticotropin on the production of increased diabetic retinopathy, the probable role of abnormal mucoid metabolism and adrenal dysfunction, and the possible effect of abnormal enzymatic processes on the mucopolysaccharides.

Cristini and associates [57] studied the polysaccharides in the platelets of peripheral blood in a group of diabetics with and without retinopathy. Severe qualitative changes, especially among patients with retinopathy, were found. The authors concluded that both the platelet alterations and the changes in the serum glycoprotein fractions played a pathogenic role, predisposing to the vascular and hemorrhagic manifestations as well as to the onset and evolution of the retinopathy. D'Esposito [58] found a small increase in the glycogen content of the rabbit's retina after 10 days of treatment with 100 mg. of cortisone given daily but a marked increase after 10 days of treatment with 20 I. U. of corticotropin given daily. Alagna [59] called attention to an increase in the mucoproteins in blood and urine among patients with diabetic retinopathy.

Franklin and Weissman [60] reported on a diabetic patient who had lipemia retinalis and xanthomas and whose serum lipids were measured. There was a marked elevation of all the serum lipids, especially the neutral fat fraction but less so the phospholipid fraction. There was a gradual reversion toward normal. The exact cause of the lactescence of hyperlipemic sera seen in lipemia retinalis is still unknown. Marty,[61] on the premise that among diabetics the vascular complications are due to lack of the lipocaic factor (a hormone produced by the alpha cells of the pancreas), treated patients who had diabetic retinopathy with Lipormone (Choay), which contains this lipocaic factor. Thirty per cent of his patients improved, fifty per cent did not change, and only twenty per cent deteriorated further.

Bietti [62] found that if persons who were breathing normal air were made severely hypoglycemic neither their light perception nor their dark adaptation was disturbed. Hyperoxia, likewise, did not change these functions. Anoxia, however, caused a decreased sensitivity to light which was partially restored by inhalation of oxygen. The hypoglycemia of fasting subjects had no effect on sensitivity to light. Berggren and Brolin [63] were unable to produce capillary aneurysms in the retinas of alloxan-diabetic rabbits kept for one month in a pressure chamber at a simulated height of 8000 meters.

Wolter and associates [64,65] demonstrated beautifully the pathologic retinal findings in patients with diabetes.

Therapy.—In answer to a query,[66] it was pointed out that the treatment of diabetic retinopathy still is not satisfactory and consists solely of control of the sugar in the blood and urine. The use of a high-protein diet for patients who have low levels of serum albumin was discussed, and it was said that some remissions in retinopathy have been reported. Neither phenylpropanolamine hydrochloride (Propadrine) nor cyanocobalamin (vitamin B_{12}) was considered effective.

Skouby [67] analyzed data on 286 diabetics whose disease began before the age of 40, between 1924 and 1954. Some were prescribed a controlled diet and some were ingesting a free diet without sugar. The general prognosis for retinopathy was much

worse among those who were given a free diet. Brétan and Oblatt [68] considered highly promising the effect of daily doses of 25 mg. of methylandrostenediol (Neosteron) upon diabetic retinopathy and carbohydrate tolerance.

Luft and associates [69] hypophysectomized 20 patients between the ages of 20 and 33 years who had severe diabetes mellitus. Two died postoperatively, and five died later. The surviving 13 patients were followed for 3 to 43 months. The retinopathy became worse in only one patient. Vascular neoformations regressed in five patients. No definite conclusions were made concerning the value of the operation. Gordon [70] reported that in his hypophysectomized patients retinopathy cleared significantly and visual acuity improved. He stated that insulin requirements were decreased by 50% to 80%.

Hypertensive Disease

Essential Hypertension.—Lockhart [71] discussed the grading of the retinal vascular changes and the classification of hypertensive patients according to the manifestations in the retina. Doggart [72] discussed examination of the fundus and its importance as a guide to hypertensive disease and its prognosis. He suggested that three major groups of vascular abnormalities are to be noted: those that are confined to one eye, those that may be related to changes in the other eye, and those that are associated with systemic disease. Klien,[73] in reviewing this article, discussed further the changes of hypertensive disease. Weekers [74] noted that choroidal arteriosclerosis, unlike retinal arteriosclerosis, is a purely ocular condition of hereditary degenerative character and does not produce generalized angiopathy.

Zozulia [75] examined 653 patients with hypertension and among them found 12 who had papilledema with retinal hemorrhage and a star figure in the macula. They had brain tumors, infectious diseases of the central nervous system, or tuberculomas. The author emphasized that a star figure in the macula does not necessarily imply renal disease, as in all 12 renal function was normal. Bessiere [76] stated that retinal hemorrhages, exudates, and edema never develop in nephrosis; they are seen frequently in nephritis but do not have any prognostic value. On the other hand, changes that occur in the blood vessels themselves have great value in prognosis. Cucco [77] performed renal biopsy on 23 subjects affected with arterial hypertension and found that the changes in the kidney did not correspond to those in the retina. He concluded that the retinal changes in arterial hypertension must be considered of dynamic origin, related to spasm of the vessels.

Puig Solanes and associates [78] compared the ophthalmoscopic findings with the postmortem pathologic findings in 90 patients who had hypertension. The retinal edema was greater in chronic glomerulonephritis than it was in essential hypertension. Retinal changes are caused by diastolic hypertension and not by renal disease. The ophthalmoscopic pictures of patients who died of cardiac, central nervous system, or renal disease were quantitatively and qualitatively the same. Correlation was moderate between the intensity of retinal angiosclerosis and the degree of renal vascular sclerosis and also between retinal angiosclerosis and progressive increase in heart size. Vigorelli and Zanotti [79] found a parallel between acoustic function and the degree of retinal vascular change in patients with hypertensive retinopathy, Keith-Wagener Groups III and IV. De Laet and Hubinont [80] found a definite relationship between measurable retinal arterial hypertension and increased flicker-fusion frequency (by the Krasno-Ivy test) but did not consider the test of clinical value unless considered with other parallel tests. It was not reliable for prediction of preeclampsia.

Takeuchi [81] showed that the retinal arterioles definitely narrow as the state of essential hypertension advances and that there is no initial dilatation as claimed by Badtke. The cause is suggested as being vasospasm. Ōoka and Ogami [82] showed that

the rise of pressure in the retinal arteries lags behind the rise in the brachial arteries when the cold pressor test is given. Recovery occurs in the same sequence. Leonardi [83] administered reserpine (Serpasil) to patients with arteriosclerosis. He produced no significant lowering of the brachial blood pressure, and pressure in the retinal artery sometimes actually increased. When this drug was given to patients with hypertension, it produced a marked fall of pressure in the brachial and retinal arteries.

Hood and associates [84,85] stated that modern treatment with antihypertensive agents definitely improves the grave prognosis of patients with Keith-Wagener essential hypertension of Groups III and IV. Frayer [86] followed the retinal changes of 111 hypertensive patients subjected to total or subtotal adrenalectomy combined with the Adson or Smithwick sympathectomy. Improvement in respect to the retinopathy was noted in 78.4% of this group. Of those with Group III hypertensive retinopathy, 92% improved, while all with Group IV hypertensive neuroretinopathy improved. He noted improvement in retinopathy without corresponding improvement in blood pressure. The degree of arteriolar sclerosis seemed to have little bearing on the end-results. This conclusion is in considerable contrast with my experience with some 95 patients operated on by the Smithwick procedure alone and reported on in 1949.[87] In the latter series the degree of sclerosis was of very significant prognostic importance, as the greater the arteriosclerosis was the poorer was the outlook. Frayer ascribed the healing of retinopathy to improved blood flow caused by diminished postoperative peripheral vascular resistance.

Pheochromocytoma.—Divišová [88] described an interesting case in which a severe retinal detachment and hypertensive neuroretinopathy developed. The hypertension and the retinal changes later subsided spontaneously, and the appearance of the retina became normal. The cause was found to be a benign pheochromocytoma of the adrenal gland with intratumoral bleeding which probably inactivated the tumor. Unger [89] discussed the findings in four patients. In two the hypertensive retinopathy disappeared after successful removal of the tumors. One of these patients had homonymous hemianopsia. A third patient had neurofibromatosis and severe hypertensive retinopathy. The fourth patient died with hypertensive neuroretinopathy, Group IV. The electroencephalographic findings were abnormal in all four cases, owing to intracranial vascular abnormalities.

Toxemia of Pregnancy.—Finnerty [90] differentiated the retinal changes of toxemia of pregnancy from those of hypertensive vascular disease. De La Riva [91] expressed the belief that the changes in the arterioles can be seen prior to the appearance of measurable hypertension. Leonardi [92] found an increase in pressure in the retinal-intracranial vascular system during the final stage of pregnancy. A certain degree of hypotension became evident in this same system during the puerperium. De Laet and Hubinont [93] said that comparative consecutive measurements of pressures in the retinal artery are of value in this condition.

Sadowsky and associates [94] studied 176 cases of toxemia of pregnancy, of which 110 were mild and 51 were severe; the severe cases included the preeclamptic, eclamptic, and hypertensive conditions. The remaining 15 patients had renal disease. A close correlation was found between the severity of the toxemia and the severity of the retinal changes. Also, there was a close correlation between the degree of retinal changes and the fetal mortality. In cases of mild toxemia with Group II retinal changes the fetal mortality was 22.2%, whereas in cases of Groups III to IV retinal changes the fetal mortality rate was doubled. There were no fetal deaths in cases in which the retina was normal. The authors advised termination of pregnancy when the retinal changes are in Groups III and IV.

Heydenreich [95] found 41 cases of eclampsia and 88 of preeclampsia in a series of 9351 pregnant women. A third of these were examined ophthalmoscopically, and 17 showed typical albuminuric retinopathy with papilledema, hemorrhages, exudative foci, and vascular anomalies. Some years later these patients showed no improvement; nine showed changes in transition from benign to malignant nephrosclerosis. Treatment was unsuccessful. The author expressed the belief that pregnancy should be interrupted as soon as toxemia with hemorrhage, papilledema, and arterial constriction and narrowing are noted.

Palich-Szántó [96] observed attenuated arterioles and numerous greenish round-to-oval foci beneath the retinal vessels. These were presumably areas of subretinal edema. Kranenburg [97] described two severe cases of toxemia of pregnancy in which the retinas were detached.

Retinal Vascular Disease

As in other years, much was written on the blood vessels of the retina. Many articles concern experimental procedures carried out with various drugs, and there is a large literature on occlusive disease of the retinal vessels.

Anatomy.—Wolter [98] found degenerative end-bulbs both on centripetal and on centrifugal fibers in the retina. These were situated in a cotton-wool patch. He later [99] showed that the blood vessels of the human retina are supplied by centrifugal nerve fibers coursing in the nerve fiber layer and he distinguished two types of fibers. Snodgrass [100] reported on a patient in whom a retinal vein crossed a retinal vein and on a patient in whom a retinal artery crossed a retinal artery. Collette and associates [101] injected thorium dioxide (Thorotrast) into the vascular system and obtained an angiogram which by microscopic examination revealed the capillary system of the eye, some anastomoses between the optic nerve capillaries and retinal capillaries surrounding the disc, an exclusively choroidal distribution of the intraocular segment of the short posterior ciliary arteries, and the absence of the anastomosis between the major iridial arterial circle and the choroidal arteries.

Thuránszky,[102] by biomicroscopy of the retinal vessels, found that stimulation of the preganglionic fibers of the cervical sympathetic nerves in the dog and cat causes a very marked increase of blood flow through the retina, the increase lasting as long as the stimulation is continued and being followed by relative ischemia. Circulation of the erythrocytes, however, occurs in only about 30% of the capillaries. By injection of a dye the capillary network can be rendered clearly visible, and it is then seen that an intensive circulation of fluid is taking place also in the capillaries in which there are no erythrocytes.

Experimental Physiologic Studies.—Pen'Kov and Eskin [103] developed an apparatus which works as a micrometer to measure the size of the retinal vessels. The authors claim a margin of error not to exceed 10%. De Rivas Cherif [104] measured the retinal vascular caliber by photo-ophthalmography with a 30-diameter enlargement and divided the result by the magnification figure to obtain the real caliber. The relation of arteries to veins is 2:3, and the mean disc diameter is 1.6 mm. Kapuscinski [105] found the serpentine pulsation of the retinal arterioles to be feeble or absent (1) when the arterioles are narrowed or obliterated as in retinitis pigmentosa, (2) in optic atrophy, (3) after occlusion of the central artery, and (4) when the discs are choked. This pulse remained visible in choroiditis and retinal periphlebitis and in most cases of optic or retrobulbar neuritis.

Bettman and Fellows [106] reported on factors that influence the blood volume of the choroid and retina; they used red blood cells incubated with radioactive phosphorus as tracers. This article was abstracted in last year's review. Chao and Bettman [107] continued this work. By the injection of neoprene into the carotid artery the cho-

roidal and retinal vascular spaces were filled in the cat's eye. It was found that the ratio of blood volume of the choroid to that of the retina was 37:1. This suggested to the authors that their method of measuring changes in blood volume reflected the choroidal blood volume almost entirely.

Levene,[108] by radioisotope methods, measured the blood flow in the eyes of rabbits and found a 90% increase as a result of paracentesis. Van Beuningen and Fischer [109] found the blood pulse volume to be 2 cu. mm. each pulsation. Sieker and associates [110] noted that reactivity of the retinal artery is usually impaired in chronic degenerative vascular disease, especially in hypertension, and occurs before there is clinical evidence of altered renal function.

Tsuruga [111] observed that the degree of retinal vasoconstriction caused by tobacco smoking is parallel to the content of nicotine and the speed of smoking. A long cigarette holder and a filter in the holder reduce the constriction. A moist cigarette causes more vasoconstriction than a dry one. Staenglen [112] noted that 1,4 dihydrazinophthalazine (Nepresol) methanesulfonate has no observable effect on the retinal vessels in normal man but that it dilates spastic retinal vessels for three hours, giving headache, dizziness, nausea, and general hypotony as side-effects. Rutin should be given, and also the patient should be treated while he is in bed. Šimková [113] measured the systemic blood pressure, pulse rate, intraocular pressure, retinal venous pressure, and systolic and diastolic retinal arterial pressure during the course of cerebral angiography and found no significant changes in the average pressures before and after angiography.

Zahn [114] gave protoveratrine intravenously to patients with hypertensive disease. It slowed the pulse rate and lowered the systemic and retinal blood pressure but did not change the intraocular or retinal venous pressure. He [115] gave hydralazine (Apresoline) to the same patients and found an increased blood supply to the retina and an increased retinal function because, he said, the drug decreased the peripheral vascular resistance. Zahn [116] further tested reserpine in the same patients; this drug had no effect on the pulse rate, systemic and retinal blood pressure, intraocular pressure, or retinal venous pressure but did cause narrowing and even normalization of angioscotoma. Hi [117] injected epinephrine into 30 rabbits daily or every other day. He enucleated the eyes 7 to 30 days later. The choroidal vessels dilated and the retina became diffusely edematous, opaque, and sometimes detached. Hemorrhages appeared between the retina and choroid. Pathologic examination corroborated the ophthalmoscopic findings and showed the development of new capillaries. The author suggested that these changes actually represented a form of proliferative retinitis due to disturbed choroidal circulation around the optic nerve.

Jacobson and Basar [118] measured with the electroretinogram (ERG) the effects of a new drug, nylidrin hydrochloride (1-[*p*-hydroxyphenyl]-2-[1-methyl-3-phenylpropylamino] propanol hydrochloride) (Arlidin hydrochloride) on the retinas of 30 subjects. Since it increased the amplitude of the b wave, the authors concluded that the drug was a potent vasodilator and produced an average increase in retinal blood flow of just over 32%. Brown and associates [119] found that breathing only 9% oxygen reduced the amplitude of the ERG response to stimulation with red light by more than 50%. This concentration of oxygen is equivalent to the atmosphere at an altitude of 20,000 ft.

Ophthalmodynamometry.—Weigelin [120] and von Bahr and associates [121] have written excellent discussions of the value and use of ophthalmodynamometry in evaluating the vascular system. Weigelin pointed out that the method is unreliable for evaluating the retinal vascular system but that it gives a good clue to intracranial vascular conditions. The method can be used in occlusion or thrombosis of the internal carotid, in cerebral arteriosclerosis, in hypertension,

and in vasomotor headaches. Svien and Hollenhorst,[122] Heyman and associates,[123] Hollenhorst and associates,[124] and Blodi and Van Allen [125] have called attention to the value of this procedure in determining the pathologic changes taking place in the carotid vessels.

Arterial Occlusions.—Rucker [126] discussed the ocular manifestations of some vascular disorders in the aged. He referred particularly to occlusions of the central retinal artery, thrombosis of the internal carotid artery or of the basilar-artery system, and temporal arteritis. Platt,[127] giving the Doyne Memorial Lecture, discussed various aspects of retinal vascular disease. Gibson [128] reviewed the retinal manifestations of arteriosclerosis. Bonnet and Bret [129] called attention to the value of doing tomography of the internal carotid artery on all patients who have suspected atheromatous plaques in this vessel or else have ophthalmoscopically visible atheromas of the retinal vessels. Wagener [130] discussed the pathogenesis of amaurosis fugax in relation to the following conditions: migraine, spasm secondary to local lesions in the walls of the retinal or carotid vessels, and local circulatory insufficiency. Betetto [131] reported spastic occlusion of the central retinal artery in a man 55 years of age who had Ménière's disease. He suggested a possible correlation between these two manifestations.

Ellis [132] reviewed the literature on cryoglobulinemia and reported on an interesting patient who had scleroderma and cryoglobulinemia and in whom occlusion of the central artery developed in one eye along with retinal hemorrhage and dilatation of retinal veins in both eyes. Spitsin-Yakubovsky [133] reported on a man 22 years of age who noticed loss of vision of the lower half of the eye after lifting a heavy load. The vision improved within the next 24 hours, but 1 month later there was complete and permanent loss of the lower half of the visual field. De Vincentiis [134] studied the late effects of occlusion of the central retinal artery with normal and red-free light in 14 cases. The peculiar macular disturbances which are observed are explained as results of mild inflammation of the choroid which becomes more evident in the macula for anatomic reasons.

Sachsenwager [135] reported on a 38-year-old woman who became unconscious and hemiplegic after occipital encephalography. Only the left eye showed fundus changes. The disc was white, and there was edema of the macula. Air spaces were seen in the arterioles and veins. The edema increased over the next few days, and the air disappeared. In experiments on dogs, the author showed that air emboli in the eye can be easily produced by intra-arterial injection but that it takes a great amount of air to produce them by intravenous injection. Air in the retinal vessels is visible several hours after death and can be demonstrated microscopically in flat sections of the retina.

Voisin and Juge [136] reported a case in which occlusion of a superior temporal retinal arteriole followed attempted abortion. The authors discussed the pathogenesis of this vascular accident and were undecided whether it was due to gas embolism or to arterial spasm. Zaikova [137] reported on a patient who had fat emboli in both central arteries after fracture of the long bones. A small amount of vision was preserved in each eye when he recovered.

Heck [138] made electroretinograms, before, during, and after treatment, on 22 patients who had occluded central retinal arteries. In a few cases the ERG was normal shortly after onset of the occlusion, but the responses disappeared in a few hours. If the circulation does not reestablish itself soon, the potentials disappear completely or remain at a very low level. Even if visual field and visual acuity improve greatly, the ERG findings remain abnormal. The higher the potential the greater the possibility of recovery. The author suggested that the ERG gives information chiefly about the bipolar cells. Lewis and Duane [139] made electroretinograms on five subjects during

accelerative blackouts. They found that, although pupillary light reflexes were lost, blackout did not extinguish the ERG response. The visual block was presumed to be at the level of the synapse of the retinal ganglion cell.

Stark [140] administered heparin to nine patients who had acute occlusion of the central retinal artery due to atherosclerosis. The results were promising. Weerekoon [141] used retrobulbar tolazoline (Priscoline) hydrochloride or 3-pyridinemethanol (Roniacol) followed by systemic treatment with the same substances. He has had rather remarkable results in some cases, so far as can be ascertained from the data given. The treatment is predicated on the theory that in most cases occlusion of the retinal artery is caused by spasm. Jacobson [142] claimed to have produced new vessels in the retina and changes in the arteries and veins of the retina by injecting benzyl cinnamate and vitamin A in arteriosclerotic persons. He stated that 25 of 33 patients with arteriosclerotic or diabetic retinopathy treated in this way had an improvement in visual acuity and that in 14 of 15 who had peripheral arteriosclerosis there was clinical improvement. Jean-Gallois [143] reported that the condition of patients who have chorioretinitis, amblyopia, or retinal vascular changes may improve when they are treated with nicotinic acid, glutamic acid, or a collyrium. He said many such improvements are purely functional, as the reported improvement was not observed ophthalmoscopically.

Takayasu's Disease.—Again there was an unusually large number of case reports of Takayasu's disease, the so-called pulseless disease. Ask-Upmark and Fajers [144] give a complete description of a necropsy on a patient previously reported on who had Takayasu's syndrome. They considered it a possible hyperergic reaction of structure exposed to hydrodynamic stress. Treatment was with steroids, which appeared to be of some help. They reviewed all the cases reported in the world literature since their earlier article appeared. The patient reported on by Balza [145] was a 41-year-old man with cataracts, vascular engorgement of the conjunctival and scleral vessels, mydriasis and pupillary rigidity, atrophy of the iris, retinal hemorrhages, and retinal vascular neoformation. There was a low systolic retinal arterial pressure and absence of the radial pulse. The other reports were those of Paterson,[146] Dollfus and Vigier,[147] Desvignes,[148] Müller,[149] Pallares,[150] Ostler,[151] Berzy,[152] Fejgin,[153] Gibbons and King,[154] Heinrich,[155] Panter,[156] Sen Gupta and Ghosh,[157] and two in the Russian literature.[158,159]

Temporal Arteritis.—There was a considerable number of reports of this disease in the literature. Panter [160] had two interesting patients who had temporal arteritis. The first had ptosis, optic atrophy, and associated involvement of the occipital artery and the coronary arteries. The second patient had hepatitis. Birkhead and associates [161] reported 55 cases of biopsy-proved temporal arteritis treated with adrenal corticosteroids. Local and systemic symptoms were promptly relieved. Thirty-one of the patients (56%) had ocular involvement as part of the syndrome. Twenty patients (36.4% of the whole group) had some loss of vision, including five with bilateral and six with unilateral blindness. No eyes that were blind improved. In no patients did blindness develop during treatment, in contrast to a nontreated control group, in which the percentage of bilateral blindness increased from 6% on admission to 17% at the time of dismissal. Caccamise [162] reported slight improvement of vision in one eye after intravenous corticotropin therapy for 10 days.

Lindblad [163] had a patient who had temporal arteritis and bilateral iritis. His disease lasted two and one-half years but reacted favorably to arterectomy and cortisone treatment. Palm [164] reported that cortisone, arterectomy, anticoagulants, and corticotropin had no reliable effect on the ocular symptoms in his eight cases. Irvine [165]

reported two cases, in one of which temporal arteritis started after an injection of gold chloride and proceeded to blindness in spite of treatment with anticoagulants and with cortisone given systemically. In his second case the condition started after an injection of penicillin. Stergar and Novak [166] isolated a viridans Streptococcus from the blood of a patient who had temporal arteritis. Under treatment with chlortetracycline (Aureomycin) the patient's general condition but not his vision improved. The authors considered this disease a manifestation of hypersensitivity to a bacterial antigen.

Obstruction of Retinal Vein.—Stephenson [167] noted that complete occlusion of the central vein was not amenable to treatment with anticoagulants. Twelve patients who had incomplete occlusion were treated with phenylindanedione (Dindevan), which stabilized the prothrombin activity at between 18% and 30%. Eight patients had resolution and restoration of circulation and visual acuity in from two to four weeks. Use of the drug was continued for three or four months. One of the discussers continued the treatment for periods ranging from 6 to 12 months. Several of the discussers reported poor results from this form of therapy. Hummelt [168] administered heparin and bishydroxycoumarin (Dicumarol) to 35 patients with occlusion of the central vein and branch veins. Among 18 patients who had occlusion of the central vein, only 2 improved during treatment and 1 more improved later. Of 17 patients with branch occlusion, 7 improved during the treatment and 1 improved later. He did not feel that this treatment had much to offer over no treatment at all. Senile and hypertensive patients had the worst outlook. Secondary glaucoma could not be averted by anticoagulant therapy.

Wise,[169] in an excellent article on the subject of venous obstruction, discussed the forms and etiology of macular disturbance in this condition. These include pigment proliferation, pigment atrophy, residual macular edema, macular cysts and holes, persistent macular hemorrhage, neovascularization and aneurysms, fibrosis and retinal folds, and circinate exudates arranged about clusters of aneurysms. Scorciarini-Coppola [170] had 52 patients with thrombosis of the retinal veins, including 20 patients with thrombosis of the central vein whom he treated with 3-(1-phenylpropyl)-4-hydroxycoumarin (Marcumar) and ethyl biscoumacetate (Tromexan); 78.8% improved. Visual acuity was restored completely to normal in 15 patients but remained unchanged in 9.

Schirmer [171] reported giving intravenously an extract of horsechestnuts containing vitamin B_1 (Venostasin) to prevent thrombosis of the central retinal vein. He said this treatment is of value. Urbanek and Peskir [172] recommend "Thrombo-Holzinger" for obstruction of the retinal vein. It is simple to give, as determination of only bleeding and clotting times is necessary and calcium given intravenously is an effective antidote. Selfa [173] used trypsin and heparin in various ophthalmic diseases. He tabulated excellent results in disciform keratitis and serpiginous ulcer of the cornea but obtained no effect in retinal lesions and only favorable effects in degeneration of the cornea, thrombosis of retinal branch veins, and uveitis. He uses heparin as a collyrium of 1% to 5% in cicatricial processes.

Paliaga [174] used hydroxyltryptamine experimentally by local application and by intravenous and intramuscular injection. It controls conjunctival hemorrhages but not those within the eye. Intravenously it was useful in operations on the lids and the lachrymal sac but not in hemorrhagic retinopathies. Gennaro and Romagnoli [175] treated thrombosis of the central retinal vein with trypsin. They said this offered the best outlook in patients in whom the vessel was not yet occluded. They found no help in diabetic retinopathy.

Alfano and Alfano [176] reported on six patients who had a mediastinal mass that obstructed the superior vena cava. The ocular signs included edema of the lids, face, conjunctiva, episclera, and fundus; and ex-

ophthalmos, edema of the discs, and glaucoma. All these were accentuated when the patient lay down. It is remarkable that only three of the six patients had a mild dilatation of the retinal veins, none had hemorrhages or exudates, and only one had some questionable papilledema. In two cases gleaned from the literature there were similarly few retinal changes.

François and Verriest [177] called attention to the value of dark-adapting the eye when the visual fields are examined in the presence of retinal vascular disease, as such scotopic campimetry will reveal a central scotoma more commonly in the presence of hypertensive, diabetic, and leukemic retinopathy even though the photopic field is normal. This technique is valuable in early thrombosis of branch veins, retinal periphlebitis, early papilledema, senile macular degeneration, angioid streaks, and central serous chorioretinopathy.

Chorioretinitis in Toxoplasmosis

Beattie [178] stated that 90% of patients with full-blown toxoplasmosis show chorioretinitis and 60% have neurologic signs and intracranial calcification. He said that about half have hydrocephaly or microcephaly and others have microphthalmos, nystagmus, strabismus, cataract, iritis, optic atrophy, and persistent pupillary membrane. An acquired form of toxoplasmosis is described which is characterized by lymphadenopathy, and it may be febrile or afebrile. It occurs in children and young adults. Chorioretinitis may occur in this form also. Beattie stated that the evidence is that the method of transmission is respiratory and that the incidence in the population is high, being higher among persons who handle animals. Cassady [179] and Forbes [180] reviewed the problems of toxoplasmosis. The latter reported 14 cases.

Jacobs and associates [181] drew the following conclusions about skin and dye tests for toxoplasmosis: 1. The complement-fixation test has little or no value unless the positive result develops during the course of an acute infection. 2. A dye-test titer of at least 1:64 may reasonably be expected in a person with active ocular disease. 3. An 80% correlation between skin tests and dye-test titers of 1:64 or higher exists. Ninety per cent of patients with positive skin reactions had a dye-test titer of 1:16 or higher. Thirteen of twenty-two patients suspected of having toxoplasmic uveitis responded favorably to treatment with pyrimethamine (Daraprim) and sulfadiazine. Cathie [182] supported the specificity of the dye test in man and stated that other parasites did not create confusion in the results of the tests.

Deutsch and Horsley [183] reported an extremely interesting clinical and pathologic study of an infant who was born with hydrocephalus, intracranial calcification, jaundice, and active granulomatous uveitis due to congenital toxoplasmosis proved by animal inoculation. At necropsy no organisms were found in any organ. There was extensive destruction of choroid and retina, and there was even destruction of the optic nerve in one eye.

Gibson [184] investigated the environment of this family and found cats, a dog, ducks, mice, and chickens near the home to be infested with Toxoplasma. All these animals had access to an uncovered garbage pail 30 ft. from the home, and this pail was used by several families. Borgen and associates [185] reported a similar case in which the source of infection was probably a cat.

Frey [186] reported on a 17-year-old girl with congenital toxoplasmosis whose ocular lesions healed under treatment with pyrimethamine and Supronal after treatment with cortisone and streptomycin had failed. François [187] reported on 28 patients of whom 80% had macular lesions and 20% had peripheral retinal lesions. Thalhammer [188] reported on three patients with ac-

quired toxoplasmosis, none of whom had ocular lesions. Rieger [189] reported on four such patients, but all had ocular lesions and metastatic localized encephalitis. Perkins and associates [190] noted that patients with chorioretinitis who had a negative reaction to the dye test for Toxoplasma or negative complement-fixation reaction did not improve when treated with pyrimethamine, but definite improvement was noted in those whose reaction was positive. Wolfe and associates [191] had a patient with pituitary dwarfism associated with congenital toxoplasmosis. They suggested that pituitary hypofunction resulted from Toxoplasma infection of the pituitary hypothalamus. Jensen [192] described a child with incontinentia pigmenti (Bloch-Sulzberger). The eyes on histologic examination showed extensive pigment changes and hemorrhage in the retina and proliferation of vascularized connective tissue into the vitreous. The significance of the positive result with the Toxoplasma test was unknown.

Inflammatory Diseases of the Retina

The literature on diseases of the uveal tract is reviewed in another issue, and in the present paper only the articles that pertain to the retina are included. Stanworth and McIntyre [193] discussed the etiology of uveitis and investigated 237 consecutive patients. In most cases uveitis was associated with parodontal and nasal sinus infection and with the presence of hemolytic Streptococcus in nasal and throat cultures. In younger persons there were some positive cultures for pneumococci. Venereal diseases, tuberculosis, and sarcoidosis caused only a few cases. Alvaro [194] summarized very completely the history and the etiology of uveitis.

Klien [195] described several retinal affections associated with disease of the uveal tract. The inflammatory manifestations may affect the stroma of the retina or the surface of the retina, as in retinitis serosa, or may cause arteriolitis, phlebitis, periphlebitis, and capillaritis. The degenerative lesions include retinoschisis, cyst formation, rupture of inner and outer cysts, and retinal separation. The functional disturbances are described by the author as macular edema or macular hemorrhage. She discusses these under the questionably appropriate term "angiospastic retinopathy." She calls attention to the possibility that a macular lesion of this type may be secondary to a hidden malignant melanoma in the periphery of the fundus. Diener [196] stated that retinal inflammation as in Jensen's juxtapapillary retinitis can also be seen some distance from the disc. The etiology of this disease is similar to that of other forms of granulomatous posterior uveitis.

Sugahara [197] expressed the belief that in most cases retinochoroiditis is due to tuberculosis. Miller and Smerz [198] reported on a patient in whom a severe local and systemic reaction developed the day after an intradermal tuberculin test was given. Sixteen days later, bilateral posterior uveitis developed which healed in one month. Takahashi [199] injected tubercle bacilli of the bovine type into the rabbit eye. The bacilli appeared in the circulating blood six hours later and in the lung, liver, spleen, and kidney three days later. On the fifth day they appeared in the lymph nodes and central nervous system. Grossly visible tuberculous changes may appear in some organs nine days after the injection. Miron and associates [200] presented five cases of recurrent ocular tuberculosis beginning 24 to 48 hours after local or remote trauma.

Lijó Pavía [201] expressed the belief that internal exudative retinitis is a definite disease which mainly affects young patients and is without known cause but may be a stress phenomenon. It affects the innermost layers of the retina and is always reversible. Tiberi [202] described in detail a patient who had central exudative retinopathy as well as optic atrophy in both eyes. He discussed the relation between the two conditions as well as their nature and expressed the belief that the former is

tuberculous in nature whereas the latter is due to alcohol.

Yuge,[203] Hager,[204] Fine and Gilligan,[205] Ikui and Hiyama,[206] and Bronstein[207] presented cases of Vogt-Koyanagi or Harada's disease. The first three papers discuss the relation between this syndrome and sympathetic ophthalmia. Yuge expresses the belief that all three diseases are closely related in some as yet unknown manner. He calls all three "oculo-oto-cutaneous syndromes" in which sympathetic ophthalmia requires a perforating injury to incite the disease and in which Vogt-Koyanagi-Harada disease probably requires some other type of precipitating factor.

Therapy.—The article by Nielsen and Kirby[208] summarizes the diagnostic and therapeutic aspects of uveitis of all types. The article cannot be adequately abstracted for this publication. Galvez Montes[209] and Kopec-Zaleska[210] reviewed the treatment of ocular tuberculosis with streptomycin, aminosalicylic acid (PAS), and isoniazid (isonicotinic acid hydrazide; INH). INH used alone cured only 1 patient out of 13, but 6 others improved and 6 remained unimproved. When streptomycin and PAS were given in conjunction, 6 of 11 patients treated were cured and 5 were improved.

Schupfer and Carrai[211] reported on four patients whose intraocular infection was treated successfully by intracarotid injection of penicillin and streptomycin. They used a solution of 500,000 units of penicillin with 250μg. of streptomycin dissolved in 10 cc. of a physiologic salt solution. They stated that the results have been very good. Three papers[212-214] have appeared in which sterile placenta was implanted subcutaneously, subconjunctivally, or into Tenon's capsule. All three papers reported considerable success in the treatment of such diseases as retinitis pigmentosa, myopia, retrobulbar neuritis, optic atrophy, retinal detachment, uveitis, and chorioretinitis.

The Retina in Various Systemic Diseases

Iserle[215] reported two cases in which he watched the fundus at the moment of death. In the moment of the last respiration the veins of the fundus became more filled; 20 seconds later the arterioles became thread-like and bloodless. The veins became progressively narrowed. Two minutes after death fragmentation of the venous blood took place. One minute after death the disc became porcelain-white and a grayish-yellow opacity appeared in the retina, beginning in the central area. Five minutes after death the thread-like arteries and veins were almost indistinguishable. Near the disc there was fragmentation of the blood in the veins. The disc and the edematous retina had the same color. One hour after death the retinal structure could hardly be distinguished and the vitreous became granular. Retinal edema became denser up to six hours after death but further examination was not possible, owing to changes in Descemet's membrane. Kevorkian[216,217] made somewhat similar observations and stated, "The ophthalmoscope can serve as an accurate aid in the rapid determination of circulatory arrest and may serve as a dependable guide in the institution of therapy."

Kadlecova and Lomíčková[218] studied a group of 163 children with congenital heart disease. Fifty-nine children had cyanosis of the conjunctival, scleral, and retinal structures. Thirty-eight children with patent ductus arteriosus sometimes had conspicuous arterial pulsation. In pulmonary stenosis, retinal cyanosis occurred only when systemic cyanosis was present. Only the 6 oldest of 13 children with coarctation of the aorta had characteristic tortuosity of the retinal arterioles.

Brihaye and Danis[219] described the pathologic examination of a 6-week-old infant who had extreme bilateral microphthalmos, progeria, congenital heart disease, malformations of the skeleton and cerebellum, and retinal dysplasia. The unidentified pathogenic agent was thought to have acted between the first and second months of pregnancy.

Lafon and associates[220] described the case of a 40-year-old man with chronic

alcoholism and total lack of gastric chlorine who had persistent retinal hemorrhages. As these responded to thiamine treatment, the authors considered them as comparable to the cerebral hemorrhages described in the classic Wernicke syndrome. In this case there were no neurologic or mental disorders.

Cambiaggi [221] described bilateral macular lesions which appeared during the course of systemic lupus erythematosus in a young Negro woman. Bonnet [222] reported on four patients with periarteritis nodosa. There was edema of the retina along with small nodules and microaneurysms of the arterioles. Le Grand, Baes, and Payfa [223] noted that in 20% of the cases reported there are ocular lesions, with more frequent involvement of the small ciliary or choroidal arteries than of the retinal arteries.

Infections.—Battistini [224] reported on a 47-year-old woman with endocarditis lenta who had visual disturbances and a preretinal hemorrhage in the macular region. The author entitled his paper "Septic Retinitis of Roth." It might be well to call attention to a translation of the original description by Roth of the spots later called "Roth's spots." [225] These spots in fact were described by Roth as small white fluffy patches rather than hemorrhages, as described in Battistini's article. Christensen and associates [226] reported a case of cytomegalic inclusion disease. This is presumably a viral multisystemic disease which appears predominantly in infants. It may be confused with toxoplasmosis because of the cerebral calcification, the retinopathy, and the cataracts that may be present.

Krauss [227] examined 40 patients with pappataci fever. The first changes in the retina occurred on the second or third day of the disease. Thirty-three of the forty had changes in the retina. There were sharply demarcated gray-white patches in the retina near the bifurcations of both the arteries and the veins. There were no optic disc or visual changes. Two to four days after the fever subsided the eyes cleared up. The changes were thought to be due to entrance of plasma into the retina and the central nervous system resulting from increased capillary permeability caused by the disease.

Büttner-Wobst [228] examined 99 children who had syphilitic mothers and found 5 of these with fundus changes ("pepper and salt" fundus in 4 and choroiditis in 1). Malhotra [229] and Lewallen [230] each described a case of exudative retinal detachment probably the result of orbital cellulitis. Gärtner [231] reported on a 52-year-old man with disseminated mycosis fungoides in whom severe conjunctivitis, corneal infiltrates, and ulcers developed. At necropsy specific infiltrations were found in the cornea, in the conjunctiva, and especially in the choroid at the posterior pole. Bonhoure [232] reported on seven patients infected with various forms of rickettsiosis in whom ocular lesions developed. There was one case of scrub typhus, three of boutonneuse fever, two of murine typhus, and one of undetermined origin. In five of these cases there was an opticochiasmal arachnoiditis. In addition, several patients had lesions of the choroid and two had retinal detachment. The author expressed the belief that Harada's disease is a manifestation of scrub typhus and that many cases of meningouveitis are probably of rickettsial origin.

Tuberculosis.—Rosselet and Magnenat [233] advised puncture of the liver to give information as to the tuberculous origin of uveitis. The liver seems to be involved in a surprisingly large proportion of tuberculous patients. Carli and Huraux [234] found primary tuberculosis in 8000 army youths, of whom 12% had fundus lesions. Jelonek [235] studied 210 children convalescent after tuberculous meningitis and found atrophy of optic nerves in 7.6%, changes of the fundus in 19%, healed tubercles of the choroid in 8%, normal eyegrounds in 63%, impairment of the nervous system in 19%, and involvement of the acoustic organs in 7%.

Minton [236] reported on four patients with tuberculous meningitis, in all of whom the presence of papilledema was a marked feature. One patient had miliary tubercles in the choroid. All except one recovered good vision. Illingworth [237] observed choroidal tubercles in 74% of 74 children whose thoracic roentgenograms showed miliary tuberculosis but in only 11% of 113 children whose thoracic roentgenograms did not show miliary mottling. Forty-one per cent of children with tuberculous meningitis had papilledema. Calmettes and associates [238] reported two cases of tuberculous optochiasmatic arachnoiditis, and Alajmo [239] reported on 50 patients, among whom those treated with cortisone seemed to have the fewest visual complications.

Parasitic Diseases.—De Gennaro [240] described infestation of the eye in man with Acarus, Actinomyces, ameba, Ancylostoma, Ascaris, Aspergillus, Blastomyces, Cysticercus, Echinococcus, Filaria, trematode larva, fly larva, and Sporotrichum. This list affords an excellent differential diagnosis in the often rare disease observed in the eye. In a symposium on the subject, Amaral Filho [241] discussed the protozoan diseases; Da Silva,[242] the action of worms, and Santiago Malta,[243] the ocular diseases produced by arthropods. Protozoans and protozoan infestations that affect the posterior segment of the eye include Giardia lamblia, leishmaniasis, trypanosomiasis, yaws, leptospirosis, rat-bite fever, and malaria. In hookworm disease there may be retrobulbar neuritis and retinal hemorrhage, and in trichinosis there may be optic neuritis, while many other parasitic worms cause damage to other parts of the eye. Intraocular myiasis caused by fly larva produces a tissue reaction in the posterior segment resembling retinoblastoma.

Braley and Hamilton [244] reported on nine patients who had macular cystic lesions with hemorrhage associated with clinically active amebiasis. These lesions healed promptly when antiamebic therapy was given. Treatment with corticotropin and cortisone caused an increase in the hemorrhagic phase of the lesions. This very important paper is well documented, and, if subsequent reports substantiate these findings, these authors have uncovered another milestone in the elucidation of chorioretinal inflammatory diseases.

Brown and associates [245] described an interesting patient who had a juxtapapillary chorioretinitis in one eye and at the same time had proved pulmonary coccidioidomycosis. Charamis [246] described his technique of removing a cysticercus from the interior of the eye.

Budden [247,248] discussed ocular onchocerciasis. In Nigeria more than 339,000 persons are infested, of whom 19,400 are blind. In some villages 10% of the population are blind from this cause. This microfilarial disease is caused by Onchocerca volvulus, and the vector is Simulium damnosum or Simulium bovis, a fly which must have rocky-bedded rivers with perennial flow and some weeds for reproducing. The bite of the fly causes the disease. Lavier and associates [249] and Rodger [250] wrote papers on the same subject. The latter recommended treatment with typhoid-parathyroid (TAB) vaccine followed by diethylcarbamazine (Hetrazan).

Sarcoidosis.—Nelson and Schwimmer [251] called attention to the specificity of the Kveim reaction. Seventy-four per cent of 72 patients with biopsy-confirmed sarcoidosis had positive Kveim reactions. Green and Kennedy [252] stated that 50% of patients who have sarcoidosis have ocular manifestations, most of which are uveal lesions. Wegner [253] and Stupenengo and Molina [254] discussed the various manifestations of this disease.

Blood Dyscrasias.—Manchester and Giddings [255] described a case of leukemic retinopathy and unilateral exophthalmos with myelocytic leukemia. Giménez Andreu [256] described the hemorrhagic retinopathy of myeloid leukemia. Otto and Pietruschka's [257] patient had 27% of the total blood pigment in the form of methemoglobin. His erythrocytes showed increased fragility.

There were iridocyclitis and papilledema. Hannon [258] and Kennedy and Cope [259] reported on patients with sickle cell-hemoglobin disease. Hannon's three patients had sickle cell-hemoglobin C disease and in the retina had typical changes of Eales' disease. Seven of twenty patients with this disease had such changes in the retinas. There were 53 patients with sickle-cell anemia; of these, 25 (47%) had dilated and tortuous veins but none had the changes described among the patients with sickle cell-hemoglobin C disease. There were 62 patients with sickle-cell trait; only 1 of these had dilated and tortuous retinal veins. Four of the patients reported on by Kennedy and Cope had intraocular lesions of a nature similar to those described in the other paper.

Lepri and Andreani [260] reported on a patient with multiple myeloma whose presenting symptom was bilateral thrombosis of the central retinal vein. Faldi and Miani [261] had 14 patients with Hodgkin's disease. The only patient of the group who had an enlarged spleen and a reduction in the platelet count had bilateral preretinal hemorrhages. Korsten and Berneaud-Kötz [262] had a patient with macroglobulinemia and cryoglobulinemia. At first the fundi were normal, but later the veins became dilated and tortuous and finally as irregular as link sausage. The disc became edematous. Renard and associates [263] found similar changes in the retina of a patient with hyperglobulinemia.

Neurologic Diseases.—Smith and associates [264] reported on the experimental production of preretinal hemorrhage and optic nerve sheath hemorrhage in the rhesus monkey by injecting saline solution into the subarachnoid space. They concluded that these hemorrhages and those caused in patients by subarachnoid hemorrhage are due to increased venous pressure secondary to suddenly increased intracranial pressure and are not an extension of hemorrhage into the subarachnoid spaces. Bozzoli [265] stressed the occurrence of papilledema and retinal hemorrhage along with subarachnoid hemorrhage. Kizelman [266] found that three-fourths of patients with brain tumor had narrowing of the central artery of the retina and dilatation of the central retinal vein. The eye on the side of the tumor frequently had the greater changes of this type.

Zimmerman and Walsh [267] reported on a patient whose left eye had been enucleated because of blindness and a rapidly growing white granular tumor on the optic disc. The tumor proved to be an almost acellular cystic lesion containing calcific deposits, metaplastic bone, and some glial proliferation and was diagnosed as being a lesion of tuberous sclerosis. Wagner's [268] patient with tuberous sclerosis had astrocytomas in the retina, intracranial gliomas, an angiofibrolipoma in one kidney, an adenoma of the thyroid, hamartomas of the lung, hemangiofibromas of many lymph nodes, and osteitis deformans of Paget. Other reports on tuberous sclerosis were those of Arrivillaga,[269] Subirana and associates,[270] and Ricci.[271] Stokes [272] reported on seven patients with Sturge-Weber syndrome. Two had isolated choroidal hemangiomas; one had a facial hemangioma with heterochromia iridis; two had facial hemangioma with glaucoma; one had choroidal hemangioma with glaucoma, and one had facial angioma with retinal detachment and possibly glaucoma. Four of the seven had retinal detachments. In two a transient rise in the intraocular pressure of the involved eye was produced by compressing the jugular veins.

Klein [273] did simultaneous electroencephalographic and electroretinographic recordings on a 10-month-old girl with Tay-Sachs disease. He concluded that the retinal elements had normal sensory function and that the optic nerve became atrophic because of involvement of the higher visual centers. Arnould and associates [274] reported on amaurotic idiocy with cerebromacular degeneration. Freitas and associates [275] and Gilje and Nissen [276,277] called attention to an increased vacuolization probably due to lipids in many of the lymphocytes of these patients. Hoffman [278] found nonspecific convulsive patterns in electroencephalo-

graphic tracings of two children with pigmentary retinal lipoid neuronal heredodegeneration. Two healthy siblings also had abnormal tracings. Čavka [279] found that patients with retinitis pigmentosa, glaucoma, and Coats' exudative retinitis often had cerebral atrophy or hydrocephalus as determined either by electroencephalography or air encephalography. He expressed the belief that these diseases are associated with disturbances of the regulatory centers in the brain.

Fülling and Pünder [280] described the case of a 2½-year-old girl who had lymphangiectatic edema, dwarfism, microcephaly, and aural deformities. Ocular abnormalities consisted of hyperopic astigmatism, esotropia and epicanthus, pigment changes at the equator of the fundus and in the macular regions, and grayish-white spots in the nerve-fiber layer of the retina. Shubova and Konchakova [281] studied 66 patients with multiple sclerosis. Forty-eight patients had diplopia or nystagmus, and seventeen had spasm of accommodation or anisocoria. Twenty-six patients had atrophy of the optic disc. Many patients had narrow arteries and periphlebitis of the retinal veins. Parsons and Miller [282] found a lowering of the flicker-fusion frequency in multiple sclerosis. They considered this to be a more sensitive test than ordinary campimetry.

Retinal Detachment

As in other years, the literature on retinal detachment is extremely voluminous, attesting to the continued interest and advancement of this field of ocular surgery. Brockhurst and associates [283] discussed briefly the diagnosis, treatment, and prognosis of retinal detachment. They expressed the belief that the scleral buckling operation now gives some patients a 50% to 60% chance when formerly there may have been only a 10% chance. Clark [284] wrote a complete and rather extensive article, which should be read in its entirety. Rendahl [285] studied with the electroretinogram 277 eyes with retinal detachment, finding a low b potential in the areas of detachment and also a lower than normal b potential in the opposite eye, even when no detachment was present. The mean preoperative b potential was higher in those eyes that later had successful surgical results.

Etiology.—Böhringer [286] made a statistical study of the incidence of retinal detachment in a five-and-one-half-year period in a population of 800,000. There were 195 cases. Among myopes of 2 to 4 D. the frequency was seven times as great as the incidence among hyperopes, emmetropes, and myopes up to 1 D. Among myopes of 5 to 9 D. the frequency was 25 times as great. The incidence in all groups increased with age. Bargossi [287] analyzed 225 cases of retinal detachment and found that myopes were more frequently affected than others, with the greatest incidence between 40 and 60 years of age. The frequency was greatest in June and August. Of 171 patients operated on, 84.7% were cured. Jensen [288] found the incidence of retinal detachment to be much greater in the summer; he studied 646 cases.

Huerkamp [289] investigated 1065 eyes and among them found 248 eyes with tears of the ora serrata. In these cases corneal astigmatism, unilateral astigmatism, and astigmatism with oblique principal meridians were found more than twice as frequently as in normal eyes. Švec [290] noted that retinal detachment occurring during pregnancy is usually due to high myopia with degenerative changes, to toxemia of pregnancy, and to an undetermined cause. The first type should be operated on immediately, and the second and third types should be treated by termination of pregnancy. Vetter [291] described a patient with neurodermatitis in whom bilateral cataract and retinal detachment developed. The final vision was better in the eye that first had diathermy and then extraction than in the other eye, which first had extraction and then diathermy.

McGavic [292] reported the interesting case of a 61-year-old man with hypothyroidism who had a sudden onset of retinal detach-

ments in both eyes without holes and with spontaneous reattachment. This sequence occurred several times, and the detachment was always associated with chemosis of the bulbar conjunctiva. Bonavolontá [293] reported five cases of retinal detachment in Marfan's syndrome. The following were the main clinical features: marked alteration of the vitreous body, severe and lasting hypotony after diathermy, and a high incidence of hemorrhagic complications. Four of the six eyes were successfully operated upon. Etzine [294] and Aronoff [295] reported similar cases.

Maumenee [296] discussed retinal detachment occurring in association with aphakia. He suggested that abnormal attachments between the vitreous and retina, traction on the weakened retina, and possibly low-grade inflammation in the peripheral retina may be factors. Twenty-seven per cent occurred within three months after cataract extraction and were commoner after vitreous losses. Fifty per cent occurred within a year, and the other fifty per cent after intervals varying from 1 to 18 years in the two series he reviewed. He stated that cataract extraction may accelerate preexisting senile macular degeneration, hemorrhagic disciform degeneration, or myopic degeneration or that macular edema may result from hypotony, from iridocyclitis, or from vitreous detachment. Michaelson [297] described four patients who had retinal detachment. Each had a retinal hole clearly associated with chorioretinitis and attending choriocapillary obstruction.

Bonavolonta [298] reviewed 66 cases of detachment from retinal disinsertion. Only 15.1% of the patients were myopes. In 60% the disinsertion was in the temporal sector; in 24% trauma was reported, and in 18% the detachment was bilateral. Forty-two per cent had cystic degeneration of the macula, and in only 18% was successful operation followed by improvement of central vision.

A symposium on traumatic detachment of the retina was reported in the French literature.[299-304] The authors stated that direct or indirect trauma is responsible for two-thirds of the retinal detachments that occur among myopes. Fifty cases of retinal detachment among 500 cases reported [300] were traumatic. In these cases, the tear generally consisted in a disinsertion of the retina at the ora serrata.

A large number of papers discussing cystic degeneration of the retina are of interest. Zucolli [305] described two types of primary retinal cysts: peripheral cysts of the ora serrata and cysts of the posterior pole. Hruby [306] showed beautiful illustrations of cysts of the choroid and retina. The former are rare. In the retinal periphery there were (1) primary schisis of the retina with ruptures of the inner layers, (2) primary schisis with cyst formation, and (3) cystic detachment of the retina. In the macular region there were (1) intraretinal cysts of the macula, (2) cyst-like serous detachment of the retina, and (3) smaller circumscribed detachment of the internal limiting membrane of the retina and of the posterior face of the vitreous. He recommended that cystoid macular edema be treated with retrobulbar injection of atropine.

Adams [307] found pars plana cysts in 1 eye of 11 eyes studied, and these were associated with cystic degeneration of the adjacent retina. Grignolo and associates [308] reported extensive cysts in this area in 26 eyes of 20 patients, and they reported a pathologic examination of 1 of these eyes. They expressed the belief that an essential etiologic factor is traction on the ciliary epithelium of the pars plana. Everett [309] examined the retinas of various animals and found that all had peripheral cystic degeneration of the retina or proliferation and schisis of the epithelium of the pars plana. Underlying these areas there were thinning and proliferation of the pigment epithelium of the retina.

Hart [310] noted the following clinical features of retinoceles: small peripheral field defects, clear vitreous, no holes, one or two dark veins, an orange-skin effect, striations, and glittering silvery spots. The condition does not seem to be progressive. Pau [311] expressed the view that these so-called cystoid

areas were in reality artifacts resulting from histologic preparation. He differentiated between these changes and the vacuoles that are precursors of retinal detachment and are also found in the detached retina, in cyclitis, and in other pathologic processes.

Wadsworth [312] presented a beautifully illustrated and annotated discussion of the changes that occur in the vitreous owing to age and disease and the effect of changes in the vitreous in producing retinal detachment. Teng and Chi [313] demonstrated with beautiful illustrations their belief that the two main anatomic factors in the etiology of idiopathic retinal detachment are liquefaction of the vitreous and vitreoretinal adhesion. They expressed the belief that the motion of fluid vitreous may, by its momentum, cause tears in the retina at the site of a vitreoretinal adhesion. Pau [314] demonstrated membranoid condensations of the vitreous which were adherent to the retina, and the adhesion consisted of a vasculoconnective tissue with abundant pigment. When the tear appears, it usually occurs at the posterior edge of this sclerotic retinal zone. Favre and Goldmann [315] discussed the same subject from the standpoint of their studies. Bedell [316] presented Kodachrome photographs of several cases of fibrous proliferation into the vitreous.

Pathology.—McGavic [317] examined pathologically an eye operated on for retinal detachment by scleral resection. The retina had reattached to the choroid by several chorioretinal adhesions resulting from diathermy. The sclera was buckled by the lamellar resection, and the retina was elevated over this buckled area. Considerable scleral necrosis and inflammation in the area of scleral resection were found. Tamler [318,319] examined eyes enucleated after previous detachment operation by diathermy or scleral resection and reported the histologic findings.

According to Alajmo and Cilento,[320] histamine was found in the subretinal fluid of some but not all cases of retinal detachment. Auricchio [321] noted that separation of the retina from the choroidal vasculature caused intraocular acidosis. Reichling [322] examined the subretinal fluid in retinal detachment by paper electrophoresis and by electronic microscopy. He concluded that not vitreous but a transudation from the capillaries forms this fluid. The causative factor, he thought, was the contact of the vitreous with the pigment epithelium of the retina or with the lamina vitrea in cases of retinal tears.

Surgical Techniques.—Parry [323] discussed some principles in the surgery of retinal separation. He stated that recent developments are directed toward bringing the retina and choroid in contact when this cannot be achieved by posturing or evacuating the subretinal fluid. He said that Arruga favors use of intravitreous air, and Weve prefers vitreous or, if this is not available, air, with scleral plication as a last resort. He went on to say that Schepens infolds a plastic tube in the line of his scleral resection. The author, Parry, infolds a lip of sclera by a special method of suturing. He also mentioned the method of light coagulation employed by Meyer-Schwickerath.

Amsler,[324] on the 35th anniversary of Gonin's original report on the pathology and pathogenesis of retinal detachment, reviewed the modern techniques to see what parts of Gonin's recommendations are still employed. These parts are (1) the importance of meticulous ophthalmoscopy before and after operation, (2) the preeminence of the retinal tear in the etiology and the importance of exact closure, and (3) the importance of preoperative and operative approximation of choroid and retina.

Marin-Amat [325] advocated extensive diathermy coagulation with drainage of the subretinal fluid in preference to scleral resection. The older the detachment the more extensive should be the coagulation. Salgado Gómez [326] stated that scleral resection is contraindicated in nonprogressive myopia of up to 6 D. and is indicated in malignant myopia or as a prophylactic operation against retinal detachment in cases of extraction of the lens.

Sjögren [327] obtained a favorable result in 12 of 19 cases of severe retinal detachment in which he performed lamellar scleral resection. Gasteiger [328] analyzed 87 cases of retinal detachment treated by the Lindner penetrating lamellar resection. In 36 eyes the retina was completely reattached, and in 6 the condition was improved. This technique has greatest value for large detachments without detectable tears, aphakic detachments, and cases of previous operative failure. Barraquer-Moner and Muiños Simon [329] reported satisfactory results with lamellar scleral resection in 73% of patients with high myopia and in 82% of patients with retinal detachment. Barraquer-Moner [330] reported on 205 cases of scleral resection for degenerative myopia. He uses this technique also for retinal detachment in aphakia, vitreous retraction, large disinsertions, failure of the retina to settle despite rest in bed, binocular bandaging, and retrobulbar injection of hyaluronidase. Also, he uses it for recurrences after classic diathermy operations or in senile detachment with extensive retinal degeneration.

King [331] noted that scleral plication has certain advantages over scleral resection in that it is easier to do when the sclera is friable owing to previous diathermy and it can be done farther posteriorly or, if necessary, in an anteroposterior or oblique direction. Sturman and associates [332] concluded from experiments on rabbit eyes that scleral-tucking procedures have great merit, as the tuck remains in place at least 12 weeks and begins then to form a solid union. Maeder [333] did 20 scleral buckling operations on patients with a poor prognosis, and 15 were successful. Shafer [334,335] reported on the use of 72 implantations of sterile human vitreous in 64 eyes with complicated retinal detachments previously unsuccessfully treated by retinal operations. The retina reattached in 29 (40%) of the 64 eyes. Pischel and Clark,[336] in commenting on the foregoing paper, agreed with Shafer's statements as to the efficacy of vitreous implants. Pischel also adds air to the vitreous cavity to prevent the transplanted vitreous from leaking out through the retinal hole.

Meyer-Schwickerath [337] again discussed his method of treatment of retinal detachment by light coagulation with a special arc lamp. Kettesy [338] used the sun as a source of light in treating a retinal detachment and macular hole; he exposed the affected eye for one minute to bright sun at noon while the patient wore a fully correcting −14 D. lens. This exposure was then repeated while the patient was wearing a −10 D. lens to cause a reaction on the detached retina itself, and, finally, a third exposure was done without any spectacles. Then the patient was wheeled into the operating room, and the subretinal fluid was drained. An excellent result was obtained. Etienne [339] advocated radiotherapy when the vision remained poor after good anatomic healing of a retinal detachment. In three cases he obtained an increase of the visual acuity and a disappearance of the macular edema and the proliferating retinitis. Verdaguer [340] discussed the complication of postoperative uveitis in postoperative retinal detachment.

Results of Surgical Treatment.—Fison [341] interestingly discussed the current methods of treatment of retinal detachment. Cramer and associates [342] reported a cure rate of 59.6% among 52 patients operated on by various methods. Coppez and Szucs [343] reviewed the results of 243 operations performed for retinal detachment. Diathermy coagulation with the pyrometric electrode led to complete recovery in 54.7%, anatomic recovery in 22.4%, and failure in 22.8%. Patients aged 61 through 70 years had a recovery rate of 47.7%, but those aged 71 through 80 years recovered in only 20% of cases. Sixty-six per cent of patients with bilateral detachments recovered, and forty-two and one-half per cent of those with traumatic detachments were cured. Only two of nine patients who had retinal detachment and ocular hypertension were cured.

Asayama and associates [344] reported cures of 66% in late cases but cures of 77% in earlier cases. Success was obtained in eyes

without retinal tears in only 39% and in aphakic eyes in only 25% of patients. Gemolotto [345] stated that, as observed in 280 cases of retinal detachment, the retina has a tendency to reattach itself spontaneously and that even those that do not gain from rest may have good operative results. Custodis [346] reported a cure rate of 83.3% among 515 patients operated on. His technique is first to do diathermy over the retinal breaks. Then over the areas of the breaks he fastens small round pieces of plastic with double-armed mattress sutures. In eight of his patients endophlebitis developed; this, he thought, was due to the plastic. If the intraocular pressure rises after the buckling, he does a paracentesis. He enforces rest in bed for one to three days and then has the patient use pinhole glasses.

Tumors of the Retina

Dunphy,[347,348] in the Gifford Memorial Lecture, discussed the treatment of intraocular malignant lesions. As this is a summary article, it cannot be well abstracted and should be read in its entirety. He and his associates [349] emphasized that the use of radioactive phosphorus in the detection of intraocular neoplasms is only a diagnostic aid and not a positive diagnostic test. They stated that a negative result does not rule out malignant disease, whereas a positive result is highly suggestive. This same point of view was expressed by other authors.[350-352]

Reese [353] discussed the differential diagnosis of malignant melanoma. The presentation is an interesting one and should be read in the original. Kirk and Petty [354] reported on 228 eyes with malignant melanoma of the choroid. An interesting observation is that 52% of 99 eyes containing melanomas were described clinically as showing active uveitis or posterior synechiae. Seventy-five per cent of 197 eyes histologically examined had posterior synechiae. Ninety-seven per cent of the patients with necrosis showed histologic signs of uveitis.

Van Wien and Schoch [355] described a very interesting case of metastatic carcinoma to the choroid and optic nerve of each eye. There seems to have been in addition an independent metastasis and an associated hemorrhage into one of the optic nerves. These metastatic lesions occurred eight months before the primary site, the breast, had an observable lesion. Newell and Harper [356] reported on the insertion of a polyethylene envelope containing blotting paper adjacent to a metastatic carcinoma of the choroid. This envelope was then filled with radioactive iodine (I^{131}). It is claimed that this method is far simpler and safer than other methods of treatment. Zimmerman and Ingalls [357] reported on a child who had retinoblastoma in both eyes and in whom, at the age of 10, an osteogenic sarcoma developed in the orbital and maxillary tissues. Das Gupta and Roy [358] had a case of neuroblastoma of the right adrenal with hepatic involvement and with widespread metastasis to all the intraocular structures and to the optic nerve of the right eye. Badtke [359] reported on a child who had pseudoglioma.

Retinoblastoma.—Manschot [360] and Danielson [361] discussed the difficulties in the clinical diagnosis of retinoblastoma. Goyal and associates [362] and Pou Díaz [363] presented cases of this disease. Tucker and associates [364] and Nicholls [365] presented cases illustrating the hereditary aspects of retinoblastoma. Jorge Campos [366] reported 23 cases of unilateral and 10 cases of bilateral disease. All patients were in advanced stages, and only three had cures of three years or more. Gärtner [367] emphasized the difference between retinoblastoma and medulloblastoma.

François and Poelman [368] discussed therapy and the rather poor results of combined diathermy and x-ray treatment. Williams [369] stated that he obtained the best results by applying radioactive cobalt by means of a disc, the design and the use of which are described in detail. Reese and associates [370,371] reported on the combination therapy of retinoblastoma with triethylene melamine and radiotherapy. Fifty patients

were given this treatment. In 33, the drug was given orally; in 8, intramuscularly, and in 9, by injection into the internal carotid artery. In 36% of the first group the tumor was arrested and useful vision was preserved. In the second group seven of the eight patients had a similar result and the eighth had an arrest of the tumor but no vision. The third method was used in nine patients with a poor prognosis; two had an arrest of the tumor and preservation of vision. The total dose employed was about 15 mg. orally or 6 to 10 mg. intramuscularly extended over a period of 6 to 12 months. Thrombocytopenia and leukopenia frequently develop.

Eaton and Ferguson [372] reported a case of retinoblastic teratoma of the epididymis. This lesion was thought to represent a one-sided development of teratoma. Caldwell and associates [373] reported a case of retinal anlage tumor of the maxilla. These tumors have a resemblance to the ciliary process in the eye.

Abnormal Retinal Vascularization

Wise [374] discussed in detail the problems of retinal neovascularization in a monograph on the subject which should be read in its entirety. Ashton,[375] in the Proctor Award Lecture, discussed vascular growth in the retina. This interesting paper reviews the known factors that seem to influence new growth of vessels in the retina. Ferreira [376] presented three cases of hemorrhage into the vitreous. In one case the hemorrhage was due to periphlebitis; in one it was due to trauma, and in the remaining case the hemorrhage, which was in the macular area, cleared after tonsillectomy. He discussed the various theories of origin of recurrent hemorrhages into the vitreous, mentioning tuberculosis, thromboangiitis obliterans, blood dyscrasias, infections, and endocrine disturbances. Nano and associates [377] had five cases of intraocular hemorrhage simulating retinal detachment.

Donders [378] followed 23 patients with Eales' disease treated with diathermy in Utrecht since 1939. Only 10 patients were observed for one or more years. Four of these had no recurrences. Five had recurrent lesions, four of which were coagulated again, with good results in three. He recommended that the operation be restricted to cases in which only a few vessels are affected.

Merz and Hauser [379] used surface diathermy over segments of retinal veins affected by periphlebitis which had led to bleeding into the retina. This arrested further progression of the disease in the eye operated on while the opposite eye went on to loss of vision. Solarski [380] treated 16 patients who had retinal periphlebitis with streptomycin, PAS, and nicotinic acid hydrazide. Patients with mild disease improved within two or three weeks and were cured in two to three months. Patients with disease of longer duration who had more extensive proliferation were treated as long as seven months. Sixty per cent had definite improvement; fifteen per cent had partial improvement, and twenty-five per cent had no improvement. Abrahamson and Abrahamson [381] used Iodoniacin, containing potassium iodide and nicotinamide hydroiodide to treat retinal or vitreous hemorrhage and reported material benefit.

Landau and associates [382] described a family tree of four generations in which 29 members were examined. Seven had conjunctival telangiectasis; two sisters had varicose retinal veins; three members had cavernous nevi, and four members were microcephalic idiots with Little's disease. Valvo,[383] Tour,[384] and Fracassi [385] reported cases of multiple microaneurysm and retinal hemorrhages which probably represented examples of Coats' disease. Zamorani [386] described a patient with both Coats' disease and retinitis pigmentosa. This patient also had a disturbance of fat embolism. Marinho de Queiroz [387,388] expressed the belief that the disease called "Coats' disease" is an entity belonging to the same group as eosinophilic granuloma of the orbit, Hand-Schüller-Christian disease, and gargoylism.

He stated that the foam cells, hemorrhages, granulomatous tissue, cholesterol crystals, fibrosis, and infiltration with round cells resemble pathologically the picture of xanthomatosis of the normocholesterinic group.

Degenerative Diseases of the Retina

Rieger [389] lectured on the genetics of hereditary diseases of the eye. François and Verriest [390] studied 14 cases of chorioretinal degeneration with the tests of Farnsworth. Various types of degenerative disease affected color vision in different ways. These authors [391] advised the use of scotopic campimetry to bring out field defects in various hemeralopigenic disorders, including tapetoretinal degenerations and other degenerations and retinopathies. Wolter [392] found hypertrophy and proliferation of the astroglia to be the most conspicuous reaction in advanced retinal degeneration. He [393] also studied drüsen in the pigment epithelium and observed two types: those which develop by accumulation of hyaline substance within slowly degenerating cells of the pigment epithelium and those which develop by extracellular deposition of hyaline substance beneath the pigment epithelium on Bruch's membrane.

Matteucci [394] described various retinal changes of a degenerative nature seen with the biomicroscope. Lucas and Newhouse [395] attempted to modify the course of a recessively inherited dystrophy of the visual cells of the mouse retina by giving large doses of various agents to the animals from shortly after birth. Undernourishment and *n*-propylthiouracil delayed and thyroxin advanced the onset of the degenerative changes. Certain vitamins, hormones, amino acids, and intermediates of carbohydrate metabolism had no effect.

Ohrt [396] reported on a Danish family in which 8 men had ocular albinism and 14 women showed the carrier state. The ocular abnormalities of the carrier state included peculiar grayish-brown irregular map-like patches of granular pigmentation in the peripheries and translucency of the iris. Waardenburg and Van Den Bosch [397] reported the same changes among members of a Dutch family.

Angioid Streaks.—Zaverucha [398] called attention to a family with angioid streaks. Scheie and Hogan [399] reported on 10 patients with angioid streaks of the retina. Eight of these had hemorrhagic macular degeneration. Eight had pseudoxanthoma elasticum, and two had Paget's disease. All 10 had clinical evidence of arterial occlusive disease in the lower extremities, and 6 had clinical signs also in the upper extremities. Some had aneurysms, and others had calcification of various arteries. The authors stressed the importance of these associated findings. McCaughey and associates [400] wrote an interesting paper reporting three cases of massive gastrointestinal hemorrhage occurring in pregnant women who had the Groenblad-Strandberg syndrome of pseudoxanthoma elasticum, angioid streaks, and visceral manifestations. Yatzkan [401] reported on a patient who sustained visual loss due to severe gastrointestinal bleeding associated with idiopathic thrombocytopenic purpura. Angioid streaks developed later on. Mackie [402] reported macular degeneration with and without angioid streaks occurring in the course of Paget's disease.

Oguchi's Disease.—Huber and associates [403] differentiated Oguchi's disease from atypical fundus albipunctatus with congenital hemeralopia by noting the normal ERG in the latter condition. Stein and Kikiela [404] described Oguchi's disease in a brother and sister. Both had had night blindness from childhood. The eyegrounds looked yellow and became pink only after prolonged occlusion. Occlusion of one eye alone produced a difference in the color of the eyegrounds. There was evidence of a disturbance in the nervous system as well.

Retinitis Pigmentosa.—As usual, there are a large number of reports of various disorders of development or diseases of the nervous system associated with primary

pigmentary degeneration of the retina. Wolski [405] reported a case of Laurence-Moon-Biedl syndrome associated with thickening of the frontal bone and with retinitis pigmentosa sine pigmento. Borón and Wiechowski's [406] patient had retinitis pigmentosa associated with annular narrowing of the soft tissues of the forearm and the leg and symptoms of dysfunction of the adrenal cortex. Fourcade and associates [407] reported associated hypoglycemia, polyuria, and scanty axillary and pubic hair. In Charters' [408] case retinitis pigmentosa developed after removal of the spleen for Gaucher's disease. Kornzweig and Bassen [409] noted the association of early celiac disease, progressive ataxic neuropathy, and acanthocytosis of the red blood cells. Albrectsen and Svendsen [410] reported on two siblings with baldness, pyknic tendency, syndactyly, and retinal degeneration. Sjögren [411] found 25 patients in 10 families who showed varying degrees of congenital oligophrenia, ichthyosis and erythroderma ichthyosiforme, and pyramidal symptoms along with macular and retinal degeneration. Björk and associates [412] reported five cases of hereditary ataxia.

Erdbrink [413] and Alfano and Berger [414] reported retinitis pigmentosa associated with external ophthalmoplegia. The patient reported by these authors also had associated spastic quadriplegia. The groups of patients examined by Pennetta and Pinto [415] and by Gareis and Platzer [416] had associated tapetoretinal degeneration and hearing loss. Mosci's [417] patient had drüsen of the optic discs associated with retinitis pigmentosa. Ohrt [418] reported on a 20-year-old student who had retinitis pigmentosa with macular involvement and who appeared simultaneously to have gyrate atrophy of the choroid and retina. Lombard [419] reported on a patient with retinitis punctata albescens associated with cerebellar atrophy.

Frohmann [420] and Rubino and Tiberi [421] reported on patients with apparently unilateral retinitis pigmentosa. Schenk and Pfeifer [422] studied 100 persons more than 60 years of age and found 12 who showed pigmentary changes along the equators of both eyes. In 4 of the 12 patients the visual field and dark adaptation were studied. Nothing abnormal could be found except an inversion of the color fields. Lijó Pavía and Brage [423] reported on three families with various recessively inherited degenerative manifestations in the retina.

Pirodda [424] found the protein content of the aqueous humor to be increased while the glucose and lactic acid content and the pH showed no change from normal values in retinitis pigmentosa. Wolter [425] used the silver carbonate staining methods of Del Río Hortega to demonstrate new pathologic details in a case of advanced retinitis pigmentosa. Skeehan and associates [426] refuted the statements of others and reported a case of retinitis pigmentosa in which the ERG tracings were essentially normal. Cordier and associates [427] did electroencephalography on 51 persons with tapetoretinal degeneration and found a high percentage of abnormalities in the EEG.

Trettenero [428] stated that stellate-ganglion block was of value in the treatment of pigmentary degeneration of the retina, retinal-vein thrombosis, and optic atrophy. Volckmar [429] concluded that the implantation of placenta subconjunctivally had no effect on retinitis pigmentosa, high myopia, or senile macular degeneration. Andreani and Volpi [430] noted a transient increase of sensitivity to light when Adaptinol (a carotene derivative which may act as a provitamin A and take part in the synthesis of visual purple) was administered to patients with retinitis pigmentosa. Kahnemann [431] used diphosphopyridine nucleotide (DPN) with vitamin A and concluded that this medicine was of value in pigmentary degeneration of the retina, angioid streaks, and myopia. Cuccagna [432] also used Adaptinol, which is the dipalmate ester of xanthophyll. He thought the drug to be of value. Franceschetti and associates [433] found the b wave of the ERG to be absent in retinitis pigmentosa and present in the

juvenile type of macular heredodegeneration.

Macular Lesions

Brückner and associates [434] wrote an interesting paper on the comparative examination of the macular region of various animals and the correlation of the appearance of this region with the life led by the particular animal. Chilaris and Pountjas [435] described their methods of studying macular function: (1) By having the patient fixate on the central letter of a specially chosen word, all the letters of which are of the same height, they determine metamorphopsia, and (2) they create glare for about 30 seconds with the ophthalmoscope. The normal eye recovers original vision in one minute at most after glare, but when macular lesions are present this period is greatly exceeded. Nano and Pérez [436] called attention to the value of Amsler's grid as a means of discovering functional alterations of the macula. Malkin [437] noted that normal persons have from 12 to 14 tiny capillary branches at the very edge of the foveal reflex. Half of 50 eyes with macular disease had no macular vessels present.

Sanna [438] pointed out that methods other than ophthalmoscopy are necessary to discover changes in the macula. The three fundamentals of macular vision are the minimal visible, the minimal separable, and the power of alignment. They recorded patients who had normal visual acuity but who had macular edema. The complaints were of phosphenes, translucent scotomas, paracentral scotomas, metamorphopsia, and micropsia. Fry and McDonald [439] reported two cases of peripheral malignant melanomas of the choroid in which the initial ocular complaint was caused by edema of the macula.

Foulds [440] and Ellis [441] reported cases of ectopia of the macula. Calmettes and Amalric [442] reported hereditary ectopia of the macula associated with blepharophimosis. François and associates [443] found that photopic vision was much more severely damaged than scotopic vision in a youth with Stargardt's disease, and they concluded that this was primarily a disease of the cones.

Wagener [444] discussed in detail the current concepts of etiology, histology, and treatment of central angiospastic retinopathy and central serous chorioretinitis. Because of the nature of the article, it does not lend itself to abstraction here and should be read in its entirety. Chervin [445] described what appears to have been an epidemic of central serous retinitis in a small town. Röser [446] described a case thought to be due to a brass dental plate. Basterra [447] reported four cases of the disease. Perdriel [448] had a case he considered to be of tuberculous origin. Marinho de Queiroz [449] examined three cadaver eyes and found that all had localized edema in the retina and surrounding structures, probably representing different phases of serous choriopathy.

Bokunyaeva and associates [450] described the use of oxygen, vasodilators, tissue therapy, and iodides in the treatment of senile macular degeneration. Sachsenweger [451] examined 15 patients with early macular degeneration wherein the ophthalmoscopic appearance was inconclusive. He demonstrated a scotoma by campimetry at a distance of 5 meters by using polarized light subtending an angle of 1 minute of arc and with the eyes dark-adapted for 25 minutes. Burnside [452] suggested treating macular degeneration by transplanting the inferior oblique muscle to the retromacular choroid to provide increased collateral circulation. Rome [453,454] advised treatment of senile macular degeneration with heparin given intravenously. Hilgartner [455] thought lipotropic substances (Lipotriad) of value for treatment. He also uses a low-cholesterol diet.

Toxic and Other Injuries to the Retina

There are a large number of reports of the toxic action of various chemicals and medications on the visual apparatus. Böke,[456] Böke and Janssen,[457] Jannssen, Böke, and von Eicken [458] and Janssen [459]

have called attention to the onset of optic neuritis as a toxic reaction to the administration of isoniazid and streptomycin for treatment of tuberculous meningitis. Studies on normal rabbits showed that large doses of isoniazid produced massive hemorrhages within the meninges and the floor of the brain and near the optic nerves. Intrathecal injection caused even more damage than subcutaneous injection. The damage probably was caused by direct injury of the nerve fibers or the smaller blood vessels of the optic nerve. Kass and associates [460] added two cases of apparent damage to the optic nerve caused by isoniazid, and Da Pozzo [461] discussed the toxic effects of streptomycin on the eye. He expressed the belief that optic atrophy is more likely due to tuberculous meningitis than it is to the drug used for treatment.

Verrey,[462] Wagner,[463] and Goar and Fletcher [464] described changes in the retina which apparently were manifestations of a toxic chorioretinopathy following the use of NP-207 (3-chlor-10-[2′-(N-methyl-piperidyl-2″)-ethyl]-phenothiazine-chlorhydrate). As pointed out by the authors and by Rucker, who discussed Goar and Fletcher's paper, toxic effects seem to appear when the dosage is in the neighborhood of 800 mg. or more daily, as none of 252 patients treated with 300 to 400 mg. daily at the Mayo Clinic experienced ocular defects of this nature. At the latter institution huge amounts given to rabbits, guinea pigs, or monkeys caused no changes in the ocular fundi.

Baumann [465] examined 35 schizophrenic patients given chlorpromazine and found no essential change in their dark adaptation. Edge and associates [466] found that a fundus picture resembling that of retinitis pigmentosa was produced in monkeys when 1:5-di(*p*-aminophenoxy) pentane dihydrochloride (M. & B. 968A) was given. Scoppa and De Natale [467] administered Atophanyl and produced concentric constriction of the fields and enlargement of the blind spots.

Babel and Ziv [468] noted the production of a retinal degeneration resembling human retinitis pigmentosa when rabbits were fed sodium iodate, sodium monoiodoacetate, sodium fluoride, and glycerinaldehyde. It was thought the effect might be due to the inhibition of glycolysis these drugs produce. Sorsby and associates [469] produced complete loss of function of the rabbit retina with sodium iodoacetate and less severe changes with bromoacetate. Lucas and associates [470] reported the same findings with bromoacetate [471] and with sodium L-glutamate and sodium L-aspartate. Mariani and Dugnani [472] produced retinal degeneration in some rabbits that received naphthalene by mouth.

Frandsen [473] and Pinero-Carrion [474] reported cases of toxic amblyopia resulting from digitalis intoxication. Turtz [475] reported a case of quinine amblyopia caused by the ingestion of 30 grains (1950 mg.) of quinine sulfate in 48 hours. Vision returned to normal two weeks after use of the drug was discontinued. Monninger and Platt [476] reported a case caused by quinidine. They noted a marked attenuation of the retinal arterioles during the time the vision was impaired, and the visual fields were constricted. When use of the drug was stopped, the visual acuity, visual fields, and retinal arterioles returned slowly to normal.

Cole and associates [477] reported on a patient who had bilateral optic neuritis due to chloramphenicol therapy. The patient had subacute bacterial endocarditis. The vision cleared when use of the drug was stopped. Larsen [478] reported four cases in which retinal changes developed during treatment with corticotropin. One patient had thrombosis of the central retinal vein; one had rapidly developing hypertensive changes; one had retinal hemorrhages and increased myopia, and one had macular edema. Hsiao-Lou Chang [479] reported 10 cases of transient blindness following retrobulbar injection of procaine-epinephrine as preoperative anesthesia for glaucoma operations. They ascribed the effect to the epi-

nephrine, as procaine alone did not cause any cases of this type.

Potts [480] disagrees with the present designation of toxic amblyopia, and he wishes to remove from this classification three entities: (1) methyl alcohol poisoning, because of the complex nature of this poisoning and because in severe form it causes severe retinal edema and optic neuritis; (2) tobacco-alcohol amblyopia, because it is due to a nutritional deficiency, and (3) mescaline intoxication, which probably damages the occipital cortex rather than the optic nerve. Burk [481] had a patient who had bilateral papillitis after inhaling methanol vapors. The vision became normal after a few weeks. The author mentioned several other similar cases.

Cibis and associates,[482] by repeated injection of saccharated iron oxide or after multiple blood transfusions in dogs, produced degeneration in various ocular tissues closely resembling the changes of siderosis bulbi and retinitis pigmentosa in man. Siderotic deposits were found in the retina, retinal pigment epithelium, choriocapillaris, and ciliary body of a patient who died of aplastic anemia and who had had multiple blood transfusions. They suggested that similar changes appear as a late result of intraocular hemorrhage because of iron liberated from the hemoglobin. Cogan [483] commented on this paper and stated that the early changes consist of an aggregation of iron granules in the endothelial walls of the blood vessel and that the late changes seem to be due to occlusive vascular disease in the retina. With sodium selenite Alagna and D'Aquino [484] produced toxicity in rabbits. Besides the changes in the liver and the spleen there were inflammation and degeneration of the iris and ciliary body, cataracts of the endocrine type, diffuse degeneration of the choroid and retina, and primary degeneration of the optic nerve fibers.

Moore [485] described three patients who had permanent paracentral scotomas after electric shock by 220 or 440 volts. In two cases the condition was unilateral and the homolateral pupil was smaller than that of the unaffected side. Four patients had reduced vision as a result of macular lesions following exposure to near lightning flashes. Ham and associates [486] used a carbon-arc searchlight to produce small retinal burns in rabbit eyes. They stated that the thermal threshold for minimal lesions ranged from 0.8 to 1.1 cal. per square centimeter.

Lyle and associates [487] reported two instances of experimental production, by high decelerative forces, of a syndrome of cerebral concussion with confusion, retrograde amnesia, circulatory shock, temporary loss of vision, retinal hemorrhages, subconjunctival hemorrhages, ecchymosis of the eyelids, and periocular edema. In a test pilot ejected at supersonic speed, retinal hemorrhages, cotton-wool patches, and retinal edema developed. A pilot ejected at 8 g had loss of vision lasting 10 minutes and conjunctival hemorrhage but no retinal hemorrhage. A jet pilot ejected at high speed sustained injuries similar to those produced experimentally. Klomp [488] reported loss of vision caused by pressure on the eyeball during anesthesia.

Optic Nerve

There is a very large literature on various affections of the optic nerve, some of which has already been reviewed by Lyle.[489]

Anatomy and Histology.—Wolter[490,491] demonstrated beautifully the anatomic and pathologic structures in the optic nerve head. He noted that the support of the optic disc consists not only of the lamina cribrosa, formed of connective tissue, but also of an anterior glial portion which resembles a shallow wicker basket and acts as a supporting, protecting, and nutritive organ for the nerve fibers which traverse it. Redslob [492] discussed the lamina cribrosa. Mathur and Mathur [493] spoke of the "fourth chamber of the eye" as being bounded by the hyaloid membrane in front, the lamina cribrosa behind, and the edge of the disc laterally.

Steele and Blunt [494] described the gross blood supply and the intrinsic vascular anatomy of the optic nerve and chiasma. No direct arterial anastomosis was found between branches of the central retinal artery and those from the anastomotic circle of Zinn. A dense capillary plexus in the region of the lamina cribrosa was noted to be in direct continuity with the choroidal capillary vessels. Liss and Wolter [495] examined an optic nerve after the globe had been enucleated 16 years earlier. They found two types of perivascular nerves which, they felt, are indicative of an autonomic double innervation of the blood vessels. Lijó Pavía [496] expressed the belief that the capillary plexus of the optic nerve has widespread anastomoses.

Liss [497] discussed the technique of silver carbonate staining of nervous tissue. He found four types of astrocytes in the central and lateral portions of the optic nerve: (1) fibrillar astrocytes of Marchesoni-Kolmer, (2) giant astrocytes with numerous long and powerful processes, (3) elements with one long and several V-shaped processes, and (4) very small cells with thin radiating processes forming a dense network with the third type of astrocyte. Various parts of the optic nerve, chiasma, and tract have different types of astroglia. Wolter and Liss [498] found centrifugal (antidromic) nerve fibers in the optic nerves. Miani [499] described a patient who, after injury, had one-sided mydriasis with absence of the direct light reflex and retention of the consensual reflex. He discussed the presence of separate visual and afferent pupillomotor fibers in the optic nerve.

Bembridge [500] studied the progress of myelinization of the visual pathways in fetuses and found the earliest signs at 20 weeks. Myelinization was seen before 36 weeks in the chiasm and proximal portions of the nerves, but there was a greater amount posteriorly and hardly any in the anterior portions of the nerves. Myelinization proceeds from the chiasmal end of the nerve toward the globe, and there is evidence that axons from the macular area are among the first to receive a myelin sheath.

Wiegand [501] produced casts of the shape of the optic canal with a seaweed substance. Twenty skulls were investigated, and the following conclusions were drawn: The orbital opening of the optic canal is a vertical oval; the intracranial end is a transverse oval, and the middle part is circular. A funnel-shaped dilatation of the orbital aperture of the canal facilitates mobility of the optic nerve within the orbit. The shape of the cerebral opening seems to be a good indicator of changes of intracranial pressure. Toti [502] injected air into the retrobulbar space and outlined the optic nerve as a small round shadow surrounded by a translucent zone.

Congenital Anomalies.—There are three reports [503-505] of crater-like holes in the optic disc. About three-fourths of the patients reported on in these articles had arcuate scotomas corresponding to the position of this hole. Kurus [506] and Rocha [507] discussed drüsen of the optic nerve head. Lansche and Rucker [508] reported on 14 patients who had such hyaline masses in the optic papilla. Six patients suffered a progressive loss in the visual field.

Franceschetti and associates [509] presented three cases of craniofacial dystrophy. One patient had bilateral papilledema, and another had unilateral optic atrophy. They recommended cerebral decompression as soon as optic nerve complications occur. Badtke [510] reported on the origin and manifestations of atypical colobomas of the inner coat of the eye and of the optic nerves. Wolter and Liss [511] demonstrated all stages of development of hyaline bodies of the optic nerve from terminal swellings of interrupted nerve fibers. They stated that degeneration of astrocytes may produce the same findings.

Traumatic Lesions.—Kiricenko [512] and Miani [513] reported cases of avulsion of the optic nerve. Brändle [514] reported that injury to the optic nerve was found in 0.7% of patients with injuries of the skull. He re-

ported 57 cases. Of 33 patients with typical injuries, 12 had amaurosis and 13 had severe loss of vision, while 2 had moderate and 6 had slight impairment of vision. At the end of the period of observation there were still 3 patients with amaurosis and 15 with severe, 6 with moderate, and 9 with slight impairment of vision. Half the patients improved, and in 21% there was definite improvement of vision. Three operative cases were reported. In the case reported by Carreras Durán [515] the patient had a fracture near the optic canal and probably a hemorrhage affecting the optic nerve. Martelli and Strazzi [516] operated on five patients within a few hours or in the very first days after injury, but in only two did vision improve.

Inflammatory Lesions.—Ricci [517] discussed the differential diagnosis between optic neuritis and choked disc. He emphasized the importance of the visual field examination. Yonemura [518] described cross-shaped scotomas in 40 patients who had retrobulbar neuritis. These scotomas are demonstrable only with very small targets. Pallarés [519] described cases of optic neuritis probably of viral origin associated with varicella and influenza. Also, he mentioned a case accompanied by spontaneous ipsilateral peripheral facial paralysis. Kajikawa [520] found that there is a definite delay in the secretion and resorption time of the cerebrospinal fluid in retrobulbar optic neuritis. Also, the thiamine content of the spinal fluid is lower than in normal persons.

Blatt and Athanasiu [521] studied 200 human skulls and concluded that from anatomic evidence the sphenoid sinus may be largely responsible for many cases of idiopathic retrobulbar neuritis. Mollica [522] described 26 such cases. Everberg [523] and MacCarty and associates [524] each described a remarkable case of optic nerve and chiasmal involvement by a cystic inflammatory lesion arising from the intracranial portion of the sphenoid sinus and cured by surgical treatment. Kawamura [525] discussed the variable shapes of the scotoma found in thiamine deficiency.

De Simone [526] reported on two patients in whom retrobulbar neuritis developed during an exacerbation of psoriasis. Schirmer [527] had a case of optic neuritis that appeared during the course of herpes zoster. Čajková [528] had a patient in whom optic neuritis developed during the course of epidemic parotitis. Bonnet and associates [529] reported on a patient who had furunculosis and then staphylococcic septicemia. A unilateral papillitis was caused by a large circumscribed abscess of the left optic nerve between the chiasm and the optic canal. Wenda [530] mentioned bacterial allergy in the etiology of retrobulbar neuritis. Favre [531] reported on a patient who had syphilitic meningitis and perineuritis. François and associates [532] discussed the symptoms and signs of vascular pseudopapillitis (ischemic optic neuritis). Their cases were associated with generalized arteriosclerosis and temporal arteritis.

Rose [533] and Frey [534] discussed cases of retrobulbar neuritis appearing during the course of neuromyelitis optica. The latter author on histologic examination found demyelinization and gliosis extending from the optic nerves as far back as the geniculate bodies.

Pettinati [535] and Heer [536] considered irradiation excellent therapy for optic neuritis.

Choked Discs.—Brégéat [537] wrote a comprehensive review of the problem of papilledema, including a section on the anatomy and embryology of the optic nerve and optic disc, the physiology of edema, and clinical aspects. He reviewed 1244 cases of cerebral tumor. Sencer [538] reviewed 87 cases of papilledema and concluded that "lumbar puncture is not a dangerous procedure in patients who have ophthalmoscopic findings which might indicate increased intracranial pressure. The lumbar puncture is of diagnostic value and the spinal fluid findings assist in managing such problems." In spite of Sencer's opinion, I reiterate the warnings of many previous writers with which I

agree; namely, if lumbar puncture is deemed absolutely necessary, it should be done with the very greatest of caution.

Wolter and Butler [539] examined the eyes of a patient who had papilledema. There were numerous cytoid bodies in the swollen disc and a great deal of accumulated fluid. Friedman [540] reported a case and discussed the syndrome of "pseudotumor cerebri." His report mentioned but did not stress the usually small size of the ventricles, which seems to me to be evidence that swelling of the cerebral tissues is an important cause of this condition. Also, he did not stress the importance of dehydration and salt restriction in the therapy. Thiébaut and Matavulj [541] presented six similar cases.

Merkulov [542] reported that in five cases of cerebral tumor choking of a disc was made to disappear for periods ranging from a year down to two or three weeks merely by dehydration and promotion of absorption with the aid of Biochinol, without any radical control of the neoplasm. These patients had malignant lesions in the cerebellum, brain stem, temporal lobe, and frontotemporal region. All patients died, and at necropsy it was established that choking of the disc had disappeared in spite of the fact that neoplastic growth had continued. Disappearance of choked disc, therefore, is not definitely conclusive as an argument against the presence of brain tumor, according to these authors.

Cartellieri [543] reported cases of papilledema due to encephalitis or encephalomyelitis. Feldman and associates [544] discussed the production of papilledema in the Guillain-Barré syndrome.

Optic Atrophy.—Chamlin [545] discussed the visual field changes produced by a number of orbital and intracranial lesions affecting the optic nerve. He said that compression of the optic nerve by a mass causes a peripheral contraction in addition to a central scotoma in the field. He properly emphasized that the shape of the field defect in one eye is not sufficient for diagnosis and that further studies are necessary to decide the cause of the lesion. Esente and d'Aprile [546] described pseudoatrophy of the optic discs in a child who had defective pigmentation of the choroid and defective development of the neuromotor mechanism. Alajmo [547] discussed optic nerve lesions in tuberculous meningitis and advised the use of cortisone along with antibiotics.

Armaly [548] reported on two patients with chondrodystrophia calcificans congenita punctata, one of whom had dacryocystitis. The other had congenital cataracts which were removed by needling, and following this both discs were found to be very pale. The author concluded that there was primary optic atrophy, although he noted that the pupillary reactions were normal. Reynon [549] described a patient who had a tumor of the third ventricle causing the Foster-Kennedy syndrome. Quintieri [550] reported an interesting case of cavernous optic atrophy with reduced vision, nasal hemianopsia, relative central scotoma, and normal intraocular tension. Angiography showed bilateral carotid aneurysms. Adamson and Judge [551] found optic atrophy in 21% of 651 Hong Kong prisoners of war.

Von Wolffersdorff [552] reported on a patient in whom bilateral optic atrophy followed acute gastric hemorrhages with anemia. Nelson and Weaver [553] had a patient in whom optic atrophy developed in conjunction with pernicious anemia. Gareis [554] reported on a patient with chronic lymphatic leukemia in whom bilateral optic atrophy developed after an attack of pneumonia and bronchitis probably due to a disturbance of nutrition in the optic nerves. Linhart [555] and Duke and Naquin [556] reported cases of lethal midline granuloma characterized by areas of dense cellular infiltration and other areas of severe necrosis invading the midline structures of the face, including the nose, oral cavity, sinuses, and orbits. No treatment appeared to be efficacious.

Kjer [557] reported the dominant transmission of infantile hereditary optic atrophy in which there was a continuous slow failure

of vision throughout life. Of 650 persons examined, 200 had optic atrophy. In addition to the optic atrophy there were often mild macular changes consisting of absent or irregular foveal reflexes and slight pigment disturbance. Waardenburg [558] reported further on previously described cases of hereditary optic atrophy. Sikorska [559] reported two cases of hereditary Leber's disease. Angelone [560] discussed optic atrophy in general, with particular emphasis on Leber's disease and opticochiasmatic arachnoiditis. Scassellati-Sforzolini [561] reported four cases of a condition diagnosed originally as Leber's disease but in which exploratory craniotomy revealed opticochiasmatic arachnoiditis. Niebeling [562] reported on 16 patients with opticochiasmatic arachnoiditis. All had impaired vision in at least one eye. Eleven had papilledema or optic atrophy; eight had exophthalmos, and three had ophthalmoplegia. Only one had a normal visual field, and most had concentric contraction.

Tumors of the Optic Nerve.—Dunn and Walsh [563] presented an interesting case report of a meningioma in the orbit first manifested at the age of 11 by blindness of the affected side and a visible tumor near the optic disc. Operation was refused, and the patient was not seen again until he was 28 years of age. He complained of loss of temporal vision in the remaining eye. The right eye had the same appearance as it had had 17 years previously. At operation a psammomatous meningioma invading both optic nerves, the choroid of the right eye, and the optic chiasm was partially removed. Martin and Schofield [564] presented a case of meningioma that invaded the fundus. Razumichina [565] described a meningioma of the optic nerve. Gramberg-Danielsen [566] had a patient with spongioblastoma of the optic nerve. Stankovic and associates [567] discussed the problems of optic nerve tumors.

Trzcinska-Dabrowska [568] reported on two patients with glioma of the optic nerve in whom the Kronlein orbitotomy was employed for removal. There were no recurrences at the end of a year. Reese [569] reported on an unusual tumor which replaced the optic nerve. It proved to be a medulloepithelioma (dictyoma). Milosevic and Litricin [570] reported a case of what appeared to be a primary pigmented tumor of the optic disc but proved on section to be a malignant melanoma. It was of the epithelioid type and probably arose from the peripapillary choroid.

Mayo Clinic.

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Correspondence

The Electronic Integrator for Quantitative Definition of Biological Curves

To the Editor:—I read with great interest the paper entitled "Quantitation of Extraocular Muscle Innervation," by G. M. Breinin, published in the May, 1957, issue of the A. M. A. ARCHIVES OF OPHTHALMOLOGY. It appears to me that the author does not seem to be aware of certain number of facts.

1. In 1937 I suggested [1] and since then have used integration as the only adequate method for a quantitative evaluation of irregular biological curves, especially for EEG records.

This proposal has been accepted by other authors, mainly by H. Berger, creator of modern EEG, and has been used in their research work.[2] However, the integration technique, which is laborious, is difficult to use.

2. Since 1939 I have used successively different electrical and electronic systems of integration.[3-8]

(*a*) The first apparatus, built in 1938, seems to be identical with Breinin's. A condenser being charged by the rectified voltage of the EEG is regularly short-circuited with constant-time intervals. The amplitude of each discharge represents the integral of the voltage accumulated during the charge periods. Thus, the integral of the records is expressed in the form of variations of amplitudes which can be measured on the record. I abandoned this system for the following reasons: In spite of all possible care, the charge is never perfectly linear, and the inkwriters increase that defect. Moreover, this technique requires numerous measurements of the successive amplitudes, which introduce new reasons for errors and are responsible for a great loss of time.

(*b*) Since 1938 I have used another system, the principle of which is as follows: The rectified voltage of the EEG charges a collector capacity through the intermediary of a constant-current penthode; when the charge reaches a certain well-defined value the capacity is discharged through a thyratron. In this system the amplitude of the successive discharges remains constant and only the frequency of discharge is variable. Thus the integral is expressed by the number of discharges per time unit. This technique, as compared with the former one, has two advantages: One no longer has to measure the amplitude of the discharges but merely to count them, which can be done by hand or by a computer; the same course of the charge characteristics is always used.

(*c*) By successive improvements I came to the realization of an electronic integrator based on a new principle without the disconvenience of capacitive integration: An oscillator is built in such a way that its output frequently is proportional to the integral of the voltage applied to its input; the frequencies are transformed into impulses which can be either recorded by inkwriters or counted by a computer. Thus, the integral of the voltage measured during a given time is expressed by the number of impulses during this time.

The functioning of this set-up is fast, automatic, and very precise, without any set-back to zero, whatever the time period of measures. Results are independent of the frequency spectrum of the curve.

This apparatus has been patented by the "Centre National de la Recherche Scientifique" in France and is manufactured by the "Etablissements Radioélectriques, G. Petit," Ezanville (Seine), France.

3. Since 1938 I have used the electronic integrator in my reaserch work on brain pharmacology.[3,4] In 1939 I had already worked out an EEG test enabling one to define in a quantative fashion the modifications of cerebral electroproduction produced by drugs. Improving that technique, I recently was able to establish

a standard quantitative method which can be used in any research on brain pharmacodynamics.[9,10] Thanks to the ease with which objective results are thus obtained, this method is becoming more and more known in France, where it is now applied to problems of industrial pharmacodynamics.[11-20]

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ZENON DROHOCKI
Hôpital de la Pitie
83, Blvd. de l'Hôpital
Paris 13.

To the Editor:—I have read Dr. Drohocki's letter with great interest. I certainly did not know of his work nor did our consulting engineers who are connected with major neurophysiological departments. Of course, integrating systems have been employed in electrophysiology for many years and in themselves are not unique. The particular combination of integrating and differentiating features in one instrument is I believe, unusual, although both principles have long been employed separately.

Dr. Drohocki's first integrator was of the same type as ours, and certain of his criticisms are quite valid. It is tedious to measure amplitudes, but for certain purposes it supplies the best answer. The linearity, although not perfect, is adequate and is not altered by oscilloscope presentation (we do not use the inkwriter). As a matter of fact, the method upon which Dr. Drohocki finally settled, although most ingenious, would not suit the purpose of electromyography in ocular muscle as well. His technique is excellent for the slow activity of the EEG but cannot be simultaneously displayed with the wave form. He employs statistical analysis of the frequencies before and after a given event as a separate operation. Our procedure gives a simultaneous presentation on film of the wave form and its integral and is adapted to the fast activity and high frequencies of motor units.

The third method of Dr. Drohocki avoids capacitive integration by using an amplitude-sensitive multivibrator to produce a frequency output which he then tabulates and compares on paper. The input to the multivibrator is the envelope obtained by full wave rectification of the original signal. One potential source of error in this system is the spuriously large amplitude produced by simultaneous activity of a number of motor units. This could give rise to more pulses than would separately occurring units. This is not a problem in the EEG but is definitely one in the EMG.

We plan, however, to investigate his technique for certain wave patterns of electromyography.

Recently I read of another integrating circuit (Inman-Momosse) using a continuously discharging capacitor instead of the periodic discharge of our method. This has real advantages for some comparison purposes and is less suitable for others. Again, the virtues or failings of these techniques depend on the application, as is stressed by Mr. Katz, our consulting engineer, in his letter.

Technology has much to offer in the field of quantitating data; e. g., we are now using a computing system for pulse analysis. These applications will be presented shortly, along with the complete schematic diagrams of the circuits. (Symposium on Electrophysiology of the Visual System, National Institutes of Health, Am. J. Ophth., to be published.)

I fully appreciate Dr. Drohocki's interest and his outstanding contributions in the field.

GOODWIN M. BREININ, M.D.
New York University Post-Graduate
Medical School
550 1st Ave., New York 16.

To the Editor:—Dr. Drohocki's anxiety to justify his instrument unfortunately obscures the fundamentals of the problem.

There are two basic methods of displaying the integral of a potential.

I. Assume a fixed time interval and note the amplitude rise (proportional to the integral) in this fixed time interval. At the end of the time interval, the amplitude is returned to zero and the process is repeated. Therefore, a larger amplitude indicates a greater integral.

II. Assume a fixed amplitude of integration and measure the time to reach this amplitude. When the fixed value is reached, a pulse is generated and the process is repeated. Therefore, a shorter interval between pulses indicates a greater integral.

Both methods essentially charge a condenser after rectification. Both methods discharge the condenser (Method I at fixed times and Method II after the integral has reached a fixed amplitude). Both methods have technical difficulties, but, with proper design and execution, will give the desired information. For example: 1. Linearity is essential for displaying the integral in Method I. Contrary to Dr. Drohocki's statement, extremely good linearity can be achieved with a high-gain Miller Integrator using a low grid current input tube. 2. Stability of the thyratron critical grid characteristic is essential for Method II. Stability can be achieved by using a regulated power supply and assuring that the thyratron is triggered with high signal levels.

Therefore, fundamentally, one can measure integration by noting and recording either an amplitude or a time interval between two discharges.

In practice, the method used is dictated by the particular application and its convenience to the investigator. Generally, it is easier to compare two amplitudes than two time intervals.

Dr. Drohocki used a variation of Method II. Assume he wants to integrate activity over one minute. He adjusts his time constant so that with the activity expected he gets many pulses and counts these pulses over the one-minute interval. This count becomes his method of measuring integration. To get a 1% resolution, he must have at least 100 pulses which are counted. However, this count cannot be simply placed on the record. This is a severe limitation when one is interested in continuously and automatically recording the integral. Furthermore, when one is interested in determining the integration over a shorter interval, say 0.1 or 0.3 second, 100 pulses means a pulse every 1 to 3 milliseconds. This pulse time begins approaching the deionization time of the thyratron, resulting in a portion of the activity not being integrated.

There is no "better" method. It depends upon the needs of the investigator and the interval over which integration is to be determined. For your application of measuring integration over short intervals and recording it simultaneously and automatically with the activity, Method I was chosen.

GEORGE M. KATZ,
Consultant Engineer
15 Stone Ave., Brooklyn 33.

Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

I. S. Tassman, M.D., Chairman

William E. Krewson, 3d, M.D., Clerk

Oct. 24, 1957

Recurrent Hemangiopericytoma of the Orbit. Dr. Edmund B. Spaeth and Dr. Antonio Valdes-Dapena (by invitation).

An adult man had his right eye enucleated in 1951 because of an ocular lesion which proved to be hemangiopericytoma. There was a recurrence in 1953, for which a complete exenteration of the orbit was performed. Some plastic reconstructive surgery of the orbit permitted the wearing of a prosthesis. In spite of 4000 r of x-ray therapy, a recurrence necessitated the removal of all the bony tissues of the orbit, exposing the dura. Sixteen radon seeds were implanted; this was followed in three months by recurrence of two separate lesions. These nodules were resected, and the wound was packed with 10 radium capsules, giving an estimated dosage of 5000 milligram hours. Six months later, that is, at present, the patient is again showing a recurrence which will probably prove fatal. The left eye is now immobile with exophthalmos, apparently due to intracranial extension through the middle fossa.

The morphology and significance of the pericytoma cell with regards to its position in the lesion was discussed, giving the credit to Stout for our present knowledge of this lesion. Comment was made regarding the x-ray and radium resistance of the tumor cell as well as the method of extension.

Ocular Cystinosis. Dr. William C. Frayer and Dr. Hugo E. Martinez-Roig (by invitation).

Three patients with ocular storage of cystine crystals associated with dwarfism and vitamin D-resistant rickets were reported. Crystals were found in the anterior stroma of the cornea, on the corneal endothelium, in the conjunctiva, and in the iris. Ocular cystinosis frequently accompanies the type of dwarfism and rickets seen in the Fanconi syndrome, and it is apparently the result of a disturbance of amino acid metabolism. The diagnosis should be suspected in all patients with rickets, and the corneal crystals can be seen easily with the ophthalmoscope. Recent evidence indicates that cystine storage with or without amino-aciduria can be found also in otherwise healthy adults.

The Pathogenesis of the Retinopathy of Prematurity. Dr. Francis P. Furgiuele (by invitation).

The overwhelming evidence gained from animal studies incriminates oxygen as the important factor in the etiology of retrolental fibroplasia. In view of the selective, unique response which oxygen exerts on growing retinal vessels, factors governing retinal vessel growth as yet unknown may also be responsible. This fact is of medicolegal importance. The manner in which oxygen appears to exert its effect in the pathogenesis of this disease has been discussed.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Nov. 21, 1957

The Twentieth Annual Lecture in Honor of the Late Dr. George E. de Schweinitz. Introduction by Dr. I. S. Tassman.

With each succeeding year, there are fewer among us who had the good fortune to know Dr. George E. de Schweinitz.

In the prime of his life, he was tall in stature, attractive in appearance, and pleasant in his manner. One was instantly impressed with his commending personality. He won many awards and honors for his contributions to the development of ophthal-

mology and was recognized as the Dean of American ophthalmology.

Dr. de Schweinitz was Professor of Ophthalmology at the University of Pennsylvania from 1902 to 1924, President of this College of Physicians of Philadelphia from 1910 to 1913, President of the American Medical Association in 1922, and a member of all of the ophthalmological societies in this country and abroad. He was the type of man who would have been an outstanding success in any field of endeavor.

Dr. de Schweinitz died on Aug. 22, 1938, at the age of 79 years. The first de Schweinitz Lecture was delivered on Nov. 17, 1938, by Dr. Edward Jackson on "The Development of Ophthalmology in One Lifetime," a most appropriate title.

Tonight we will hear the Twentieth Annual de Schweinitz Lecture, to be delivered by Dr. John W. Dunnington, of New York, who is well known to most of us.

Some Modern Concepts of Ocular Wound Healing. DR. JOHN H. DUNNINGTON.

This article was published in full in the March issue of the ARCHIVES, page 315.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Dec. 19, 1957

Filaria Loa. DR. R. D. HARLEY (by invitation).

Loa loa, a filaria indigenous to West Africa, is rarely encountered by ophthalmologists in this country. The fact together with the dramatic appearance of the worm beneth the conjuntiva is of interest and deserves comment.

A missionary nurse was seen June 9, 1957, because of a recurrent episode of a worm in the left eye. She had recently come from the Belgian Congo, where Loa loa was prevalent. She had been bitten by a Mangrove fly (Chrysops) in 1948. Her first symptoms of the worm's presence were in the form of migratory Calabar swellings in 1951. The patient's rest had been disturbed the entire night of June 8 by the movements of the filaria in the left eye. Upon examination the next morning it was plainly visible undulating over the sclera in the subconjunctival space. The worm was removed from the subcutaneous tissue of the left lower lid after an unsuccessful attempt to extract it from the subconjunctival space. Brief descriptions of the intermediary host, the Mangrove fly, and the parasite, Loa loa, are presented. The most effective treatment is surgical extraction of the adult worm. A suggested technique for the removal of the filaria is outlined.

Superficial Keratitis Due to Plastic Foreign Bodies. DR. T. D. DUANE (by invitation).

Approximately 75 cases of keratitis due to the presence of small flakes of Bouffant (modified nylon) on the superficial epithelium of the cornea were described. The flakes, which appear as a result of shearing of the stiff plastic material, are chemically inert and produce low-grade symptoms due to their mechanical foreign-body attributes. They are difficult if not impossible to see without biomicroscopic magnification and can best be removed by lifting them away with a spud or needle. Our experiences have been confined chiefly to garment workers, but more recently cases have appeared among the general populace. A warning is given that similar instances may appear as the material is more widely used in clothing and household decorations. Typical cases were presented.

The Use of Tenon's Capsule in Strabismus Surgery. DR. FRANCIS HEED ADLER.

Strips of Tenon's capsule may be used to pull the eyes into alignment where an ocular muscle has been cut accidentally or is congenitally absent. In three cases this has proved to be a simple and effective measure, resulting in good alignment of the eyes and, in two of the cases, complete restoration of ocular motility. This was due presumably to the inclusion of muscle fibers in the tongue of Tenon's capsule.

The paper will be published in full in the *American Journal of Ophthalmology* in the issue dedicated to Sir Stewart Duke-Elder.

News and Comment

ANNOUNCEMENTS

Asia-Pacific Academy of Ophthalmology—Tour.—The Asia-Pacific Academy of Ophthalmology is sponsoring a good-will tour to countries of the Orient following the International Congress of Ophthalmology in Brussels in September, 1958. The purpose of this tour, which is to last approximately one month, is to hold joint meetings with ophthalmologists in India, Pakistan, Burma, Thailand, Philippines, Hong Kong, and Japan. It is expected that this good-will tour will create much interest among ophthalmologists in the countries to be visited and contribute greatly to American-Asiatic medical *rapprochement*.

Our government has given its whole-hearted support to the plan of stimulating and facilitating a continuing exchange of information and techniques, treatments and devices for the care of the ill and the blind.

The reception of a group of ophthalmologists the world over will certainly be most cordial and will assure the success of this enterprise.

Ophthalmologists interested in presenting papers at these meetings should contact William John Holmes, M.D., Liaison Secretary, Suite 280 Alexander Young Building, Honolulu 13, Hawaii. Additional information regarding travel arrangements may be obtained from Compass Travel Bureau, Inc., 55 W. 42d St., New York 36.

Southern Section, Association for Research in Ophthalmology: Call for Papers.—The 1958 meeting of the Southern Section of the Association for Research in Ophthalmology will be held in New Orleans, November 11, 1958, conjointly with the Eye, Ear, Nose, and Throat Section of the Southern Medical Association.

Anyone wishing to present a paper before the Southern Section is urged to communicate with Dr. A. E. Meisenbach Jr., Secretary, Southern Section, Association for Research in Ophthalmology, 317 Medical Arts Building, Dallas 1, Texas.

An abstract of seventy-five words or less is required for publication in the official bulletin of the Southern Medical Association. A second abstract, no limit, can be submitted for publication in the Research Section of the *American Journal of Ophthalmology*. The seventy-five-word abstract for the Southern Medical Association must be received before July 1, 1958, in order to meet the deadline set by the Southern Medical Association.

Oxford Ophthalmological Congress.—The forty-third Annual Meeting of the Oxford Ophthalmological Congress will be held July 7, 8, and 9, 1958, in the Lecture Hall of the School of Physiology, South Parks Road, Oxford, England. Topics will be "The Early Clinical Diagnosis of Glaucoma," "The Aetiology and Treatment of Uveitis," and "The Influence of Vascular Changes in Progressive Failure of Vision."

Third International Congress of Allergy.—The Third International Congress of Allergy, sponsored by the International Association of Allergology and French Allergy Association, will be held in Paris, France, Oct. 19-26, 1958.

The program will include (*a*) symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, autoimmune reactions, dermatology, and socioeconomic aspects. Participants are world authorities in special fields: Pasteur Vallery-Radot, Löffler, Grabar, Dixon, Chase, Coombs, Forsham, Sir Henry Dale, Halpern, Schild, Harrington, Ackroyd, Dausset, Zendek, Sulzberger, Jadassohn, and many others; (*b*) sectional papers, limited to 10 minutes, on any phase of allergy; (*c*) round-table small-group luncheon conferences on selected

subjects led by international authorities; (*d*) pre- or postconvention tours; (*e*) social events—a very enjoyable program has been arranged.

For all information regarding the program and papers to be presented please write to the following:

United States and Canada: Dr. Samuel M. Feinberg, 303 E. Chicago Ave., Chicago.

Latin America: Dr. José M. Quintero Fossas, Paseo 313, Vedado, Havana, Cuba.

Europe and other countries: Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris 7, France.

For Congress information and registration write to Dr. Halpern at the above address. Registration fees are $32 for congressists and $15 for relatives of congressists.

Travel arrangements and pre- or postconvention tours will be handled by Thos. Cook & Son, Inc.

GENERAL NEWS

National Society for the Prevention of Blindness 1957 Research Grants

Institution & Supervisor of Research	Title of Study	Amount Granted
University of Nebraska College of Medicine, Omaha; Gordon E. Gibbs, Ph.D., M.D.	Biochemical correlates of diabetic retinopathy, serum sialic acid, urinary 17-hydroxycorticosteroid	$3800
Francis I. Proctor Foundation for Research in Ophthalmology, Univ. of California Medical Center, San Francisco; Michael J. Hogan, M.D.	Treatment of pseudomonal corneal infections	1100
Medical College of Georgia, Augusta; John R. Fair, M.D.	Bacteriology of uveitis	2000
Wills Eye Hospital, Philadelphia; Irving H. Leopold, M.D.	Choroidal circulation	3000
New York Eye & Ear Infirmary, New York; Hunter H. Romaine, M.D.	Clinical electrophysiology	2400
Washington University School of Medicine, St. Louis; Bernard Becker, M.D.	Experimental retinal lesions	4400
Boston University School of Medicine, Dept. of Pediatrics, Boston; Sydney S. Gellis, M.D.	Development of effective apparatus to test vision in early infancy by means of the optic-kinetic response	4500
University of Texas Medical Branch Hospitals, Galveston; Gaynelle Robertson, M.D.	Effect of electrolytes on eye tissue as encountered in ocular surgery	3000
Columbia University College of Physicians & Surgeons, New York; Ira S. Jones, M.D.	Experimental production of orbital changes produced by implants and by tumors	1320
Jewish Hospital of Brooklyn, New York; Mortimer A. Lasky, M.D.	Biochemical studies in human retinitis pigmentosa as compared with the normal	1980

Binocular Aphakia

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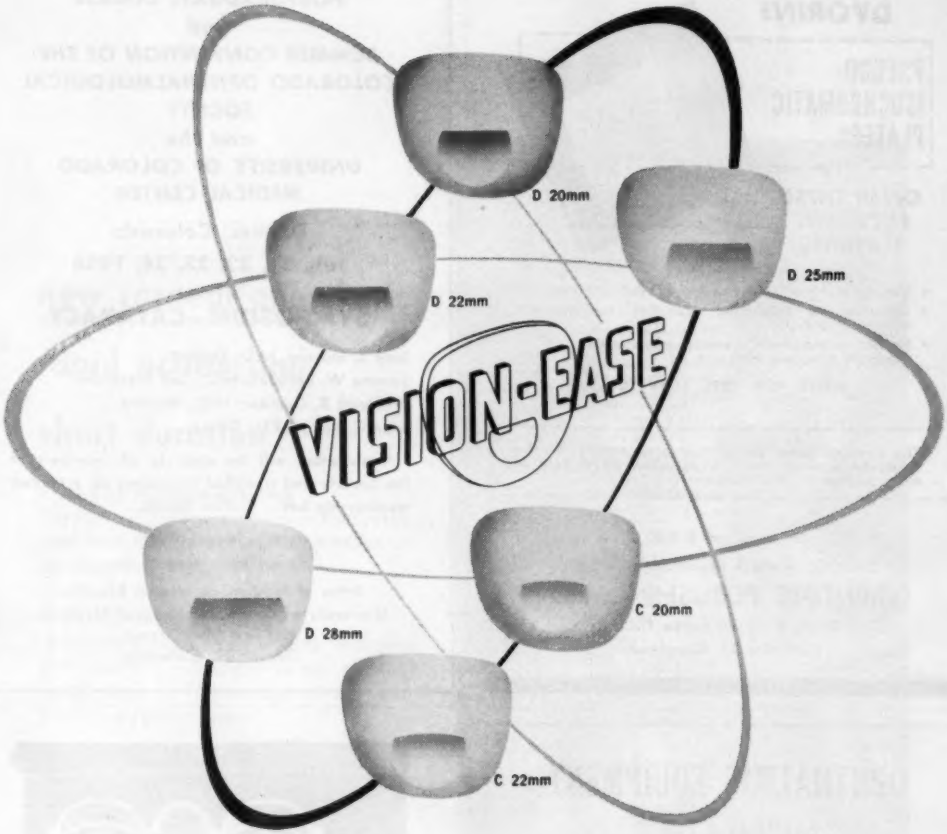

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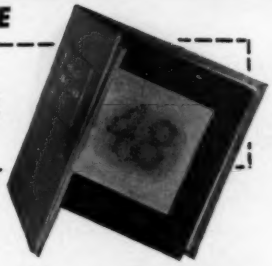

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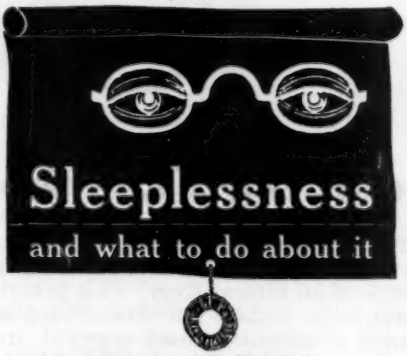

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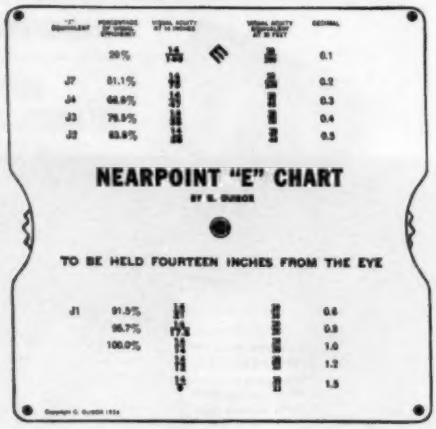

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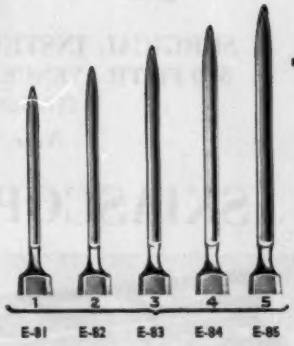

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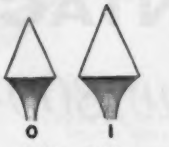

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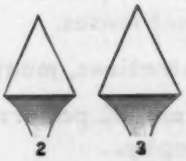

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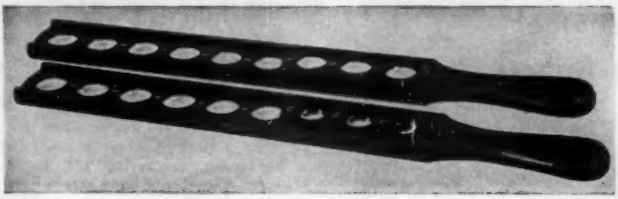

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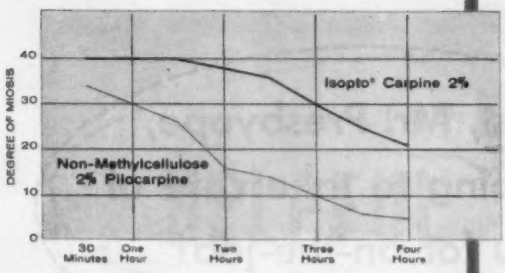

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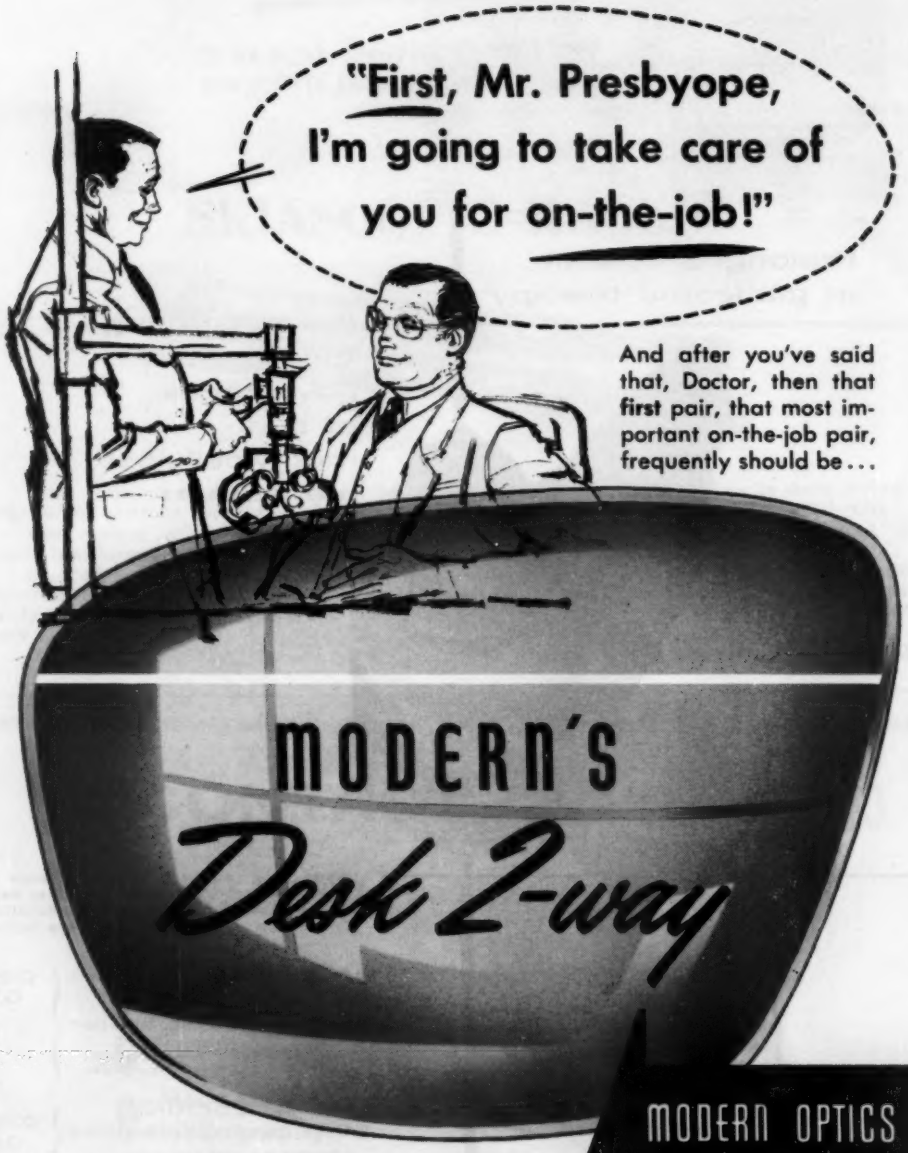
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